NEUROPSYCHOLOGICAL SEQUELAE OF PAEDIATRIC POSTERIOR FOSSA BRAIN TUMOURS: THE EFFECT ON QUALITY OF LIFE

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PREFACE

This study represents my own work and has not been submitted to any other University.

Where use has been made of the work of others, it is duly acknowledged in the text

Dedicated to the children and families who overcame their fears with courage and tenacity and showed us that life is a precious gift.

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ABSTRACT

A retrospective study from 1968 to 1996, of children diagnosed with posterior fossa brain tumours and treated at Red Cross Children's Hospital and Groote Schuur Hospital was carried out. The aims of the study were: 1) Describe the neuropsychological and quality of life outcomes after treatment with surgery, radiotherapy and chemotherapy: 2) Examine the relationship between the independent variables (age and time variables, socioeconomic status, pretreatment factors, tumour type, treatment and complications after treatment) and the dependent outcome variables using a battery of neuropsychological tests and quality of life measurements. A sample of 174 children was obtained from the hospital records. Of these 44% of the sample were deceased, 44% survived and 12% could not be traced. Fifty one subjects agreed to participate and were divided into three groups according to the type of treatment administered: Group 1 (n=12) surgery only treatment comprised astrocytomas ; Group 2 (n=20), surgery and radiotherapy treatment included astrocytomas (n=4), medulloblastomas (n=11), ependymomas (n=4) and brain stem glioma (n=1); Group 3 (n=19) surgery, radiotherapy and chemotherapy treatment were all medulloblastomas. Medical and treatment details were extracted form the records. Background information, developmental history, schooling, occupational details and current functioning were obtained from the parents and/or adult survivors. The mean Age-at Diagnosis was 7.6 years and the mean Years-since-Treatment was 8.5 years. Analysis of Variance showed statistically significant differences between the Groups on the neuropsychological test battery in the domains of: attention, visuomotor integration, memory and motor functions. Group 3 were significantly worse than the other two Groups on all the measures. Quality of Life outcome was not statistically different between the Groups but on all measures Group 3 tended to have the worst outcome (Walker Problem Behaviour Identification Checklist, Health Related Quality of Life, Educational Attainment, Height). Post hoc analysis on medulloblastoma subjects showed that verbal intelligence was significantly lower with increasing Years-since-Treatment. A significant difference was also found on prorated full scale intelligence scores between the medulloblastoma survivors treated with surgery and radiotherapy and those treated with additional chemotherapy. Overall quality of life was compromised by the treatment of radiotherapy and chemotherapy.

CONTENTS

ABBREVIATION

ALL	Acute Lymphoblastic Leukaemia
ANOVA	Analysis of Variance
AVLT	Auditory Verbal Learning Test
BBB	Blood Brain Barrier
CA	Chronological Age
CNS	Central Nervous System
CRT	Cranial Radiation Therapy
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
FSIQ	Full Scale Intelligence Quotient
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GRP	Group
Gy	Centigray
ICP	Intracranial pressure
ISX	The Individual Scale for Xhosa Speaking Pupils
LSD	(Fisher's) Least Significant Difference
MA	Mental Age
MHSC	Multiattribute Health Status Classification
MRI	Magnetic Resonance Imaging

OSAIS	Old South African Individual Scale
P	Percentile
PIQ	Performance Intelligence Quotient
PNET	Primitive Neuroectodermal Tumour
RFRT	Restricted Field Radiation Therapy
RT	Radiation Therapy
SAWAIS	South African Wechsler Adult Intelligence Scale
SC	Scale Score
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Result
SES	Socio-economic Status
SSAIS-R	Senior South African Individual Scale-Revised
TMT	Trail Making Test
TVPS	Test of Visual Perceptual Skills (non motor)
VIQ	Verbal Intelligence Quotient
VMI	Visual Motor Integration
WBRT	Whole Brain Radiation Therapy
WHO	World Health Organisation
WMS-R	Wechsler Memory Scale-Revised
WPICL	Walker Problem Identification Check List
X	Equals Means[1]

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CHAPTER 1

INTRODUCTION

"And still they gaz'd and still the wonder grew,
That one small head could carry all he knew."

Oliver Goldsmith, *The Deserted Village*

Neuropsychological assessments, by their very nature are themselves a measurement of quality of life. Quality of life, however, defies finite definition and it is perhaps simplest to understand it in the overall context of health. According to the World Health Organization (1958) "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". The dilemma that exists between the importance of the cure of the disease and the preservation of the quality of life in the treatment of children with posterior fossa brain tumours is an ongoing one which is subject to increasingly sophisticated treatment (Mulhern, Horowitz, Kovnar *et al.,* 1989, Sutton, Packer, Siegel *et al.,* 1989).

The treatment of childhood brain tumours requires a multidisciplinary team approach. Research into the quality of life of the survivors thus needs to be broad enough to include the relevant treatment dimensions such as surgery, radiation and chemotherapy together with the pre-treatment factors and post-treatment complications which may arise as a result of the treatment. An implicit consensus reached by reviewers of research on radiotherapy in children is that cranial irradiation is a risk factor for impaired neuropsychological functioning in intellectual, visual perceptual, motor, memory, emotional and behavioural functions. It also results in academic underachievement, an increased need for special educational services in school and leads to subsequent employment problems (Crossen, Garwood,

Glatstein *et al.,* 1994; Hoppe-Hirsch, Renier, Lellouch-Tubiana *et al.,* 1990; Johnson, McCabe, Nicholson, 1994; Kun, Mulhern and Crisco,1983; Lannering, Marky, Lundberg *et al.,* 1990; LeBaron, Zelter, Zelter *et al.,* 1988; Mostow, Byrne, Connelly *et al.,* 1991; Packer, Sutton, Atkins, 1989; Radcliffe, Packer, Atkins *et al.,* 1992; Ris & Noll, 1994).

With the introduction of more refined forms of treatment in the combat of disease, the usual morbidity and mortality markers become inadequate. There is now a change to the "new morbidity" in paediatrics, referring specifically to developmental, behavioural and learning disorders as well as social dysfunctions of children and adolescents (Rosenbaum, Cadman and Kirpalani, 1990).

Medulloblastoma is the most common paediatric posterior fossa brain tumour, followed by low grade cerebellar astrocytoma, brain stem glioma and ependymoma tumours (Halperin, Constine, Tarbell *et al.,* 1994). The survival rates of different types of posterior fossa tumours indicate that cerebellar astrocytomas have the best prognosis followed by medulloblastomas, ependymomas and brain stem gliomas. With the recent progress in treatment, the prognosis for patients with these tumours has improved and now about 60% of children with medulloblastoma can expect to live five years longer (Jenkin, 1996 Packer, Sutton, Atkins *et al.,* 1989). Tumour type and the associated natural morbidity are interdependent factors when investigating the neuropsychological effects on outcome. Therefore an important consideration in assessing neuropsychological outcomes is the disparity between tumour types. Ris and Noll (1994) in an extensive literature review found that many researchers had not taken this into account and commented that it was both a function of the controversy surrounding the classification and the rarity of the tumours.

The diagnosis of all brain tumours must incorporate histology findings in order to determine whether children are treated with surgery only, or a combination of surgery and adjuvant radiotherapy. Surgery only is not

usually associated with cognitive morbidity (Bordeaux, Dowell, Copeland *et al.,* 1988), nor is there clear evidence that the amount of tumour in the surgical resection is associated with intellectual decline (Ellenberg, McComb, Siegel *et al.,* 1987; Johnson *et al.,* 1994; Yang, Wong, Cheng *et al.,* 1997). Difficulty in the evaluation of the surgical resection comes from variation in surgical procedures, in the pre-treatment variables and in the intraoperative support and post-operative management.

Children with posterior fossa tumours are predisposed to hydrocephalus because of proximity to the fourth ventricle and the cerebrospinal fluid pathways (Kumar, Phipps, Harkness *et al.,* 1996). The complications caused by raised intracranial pressure, due to both the tumour and the hydrocephalus, and the diverse policies of neurosurgical departments, contribute to the difficulty in interpreting the neuropsychological results. This difficulty is exacerbated by pre-treatment factors. The duration of the presenting symptoms, the extent of cerebellar and brain stem dysfunction, and seizure activity are not well documented in the literature. Pre-treatment factors may thus play a vital role in neuropsychological outcomes and it is difficult to isolate individual contributions to neuropsychological outcomes.

The impact of non-methotrexate chemotherapy on the developing brain and subsequent cognitive functions is not clearly defined in the literature (Dowell, Copeland and Judd 1989; Jenkin, Greenberg, Hoffman *et al.,* 1995; Packer, 1999). The majority of treatment protocols are in a continuous state of flux as oncologists attempt to minimize the effects of radiation therapy (RT) on the developing brain by revising the RT doses and chemotherapy protocols. The researcher is thus faced with changes in treatment protocols over time, which are always a potential source of bias.

The complications following the treatment of posterior fossa tumours, such as transient cerebellar mutism, growth hormone deficiency, seizures and repeated shunt revision, are seldom mentioned in assessing the impact of treatment on neuropsychological outcomes.

With the change of emphasis to a holistic conceptualization of quality of life, paediatric neuropsychology needs to be defined in the broader context of child and adolescent development. This is an evolving process where the following major obstacles must be considered.

a) *The constantly changing picture of the developing child with age.* While some generalizations can be made about the adult with a specific type of lesion the effects of brain tumours in children can vary greatly with age (Mulhern 1994; Ris and Noll, 1994; Spreen, Risser, Edgell, 1995; Taylor and Alden, 1997). Different researchers have focussed on the effect on Age-at-Diagnosis (when the diagnosis of the tumour was made) and subsequent neuropsychological outcomes (Chapman, Waber, Berstein *et al.,* 1995; Dennis, Spiegler, Hetherington *et al.,* 1996; Ellenberg *et al.,* 1987; Kimmings, Kleinlugtebeld, Casey *et al.,* 1995; Moore, Ater & Copeland, 1992; Mulhern & Kun, 1985; Nishiyama, Funakoshi, Izumoto *et al.,* 1994; Radcliffe *et al.,* 1992; Silber, Radcliffe, Peckham *et al.,* 1992; Sutton et *al.,* 1989).

The relationship between Age-at-Diagnosis and resultant neuropsychological functioning is difficult to identify because of the variations in the definitions of "younger". Diagnosis at under three years old has a poor prognosis particularly when children are treated with radiation (Hoppe-Hirsh *et al.,* 1990; Johnson *et al.,* 1994; Sutton *et al.,* 1989). In addition the potential confound between Age-at-Diagnosis and the interval between neuropsychological evaluation remains a dilemma as stated in the review of Ris and Noll (1994).

The influence of the Time-since-Treatment on neuropsychological functioning is a possible confound as some effects may emerge late. Sheline (1977), describes the sequential stages of radiation reaction which can range from many months to several years with the peak

of symptoms only manifesting 6 to 24 months after cranial irradiation. Time-since-Treatment is thus a complex issue as some authors suggest progressive deterioration in FSIQ in survivors of brain tumours (Ellenberg *et al.,* 1987; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch, Brunet, Laroussinie *et al.,* 1995; Moore, *et al.,* 1992; Nishiyama *et al.,* 1994; Packer *et al.,* 1989; Seaver, Geyer, Sulzbacher *et al.,* 1994).

The relationship between Age-at-Diagnosis and Time-since-Treatment is seldom addressed. Dennis, Spiegler, Hetherington *et al.,* (1996), in assessing a group of medulloblastoma tumour survivors found that Age-at-Diagnosis and Time-since-Treatment contributed separately to intellectual morbidity.

b) *The interaction of the developing child within the environment.* Socio-economic factors impact on the quality of life. These include the home and school environment, parental education and a number of psychographics which may limit or enhance recovery (Fletcher & Copeland, 1988; Hemp, 1989; Taylor & Alden, 1997). However, the crucial role of socio-economic status (SES) on long term neuropsychological outcomes of children with brain tumours is seldom addressed (Ris & Noll, 1994).

Extensive literature reviews on children treated for brain tumours show that there is no distinct neuropsychological profile (Glauser & Packer, 1991; Ris & Noll, 1994). A pattern of deficits in attention, memory and non-verbal skills, but with relative preservation of language abilities, is found in patient populations with congenital hydrocephalus or head injury who sustain damage to the cerebral white matter. Fletcher and Copeland (1988), report the same deficit pattern in children with acute lymphoblastic leukaemia (ALL) treated with prophylactic cranial irradiation. Moore, *et al.,* (1992) reveal a similar pattern in children treated in infancy with cranial irradiation.

The early vulnerability hypothesis of various researchers proposes that widely distributed cortical and subcortical systems are important for skill acquisition in early life and that learning capacities in young children are vulnerable to brain injury (Stiles & Thal, 1993; Dall'Oglio *et al.,* 1993 in Taylor & Alden, 1997). Alternatively, treatment at a young age may limit the brain's capacity to develop normally or interfere with the timing of neural development (Jenkin, Danjoux & Greenberg, 1998). Increasing deficits over time may also be due to disruptions in the child's ability to interact with the environment at ages when these interactions are critical to further development (Fletcher, Levin & Landry, 1984). According to Spreen *et al.,* (1995) the brain-damaged child does not reflect a simple diagnostic entity, but may vary from one individual to another.

The difficulty in reaching consensus about the consequences of treatment for childhood brain-tumour survivors has in part, been attributed to variations in research methodology (Glauser & Packer, 1991; Mulhern, 1994; Roman & Sperduto, 1995; Ris & Noll, 1994). Studies differ in terms of the samples, the interval at which they were followed-up, the prospective or retrospective design, the use of control groups, the tests used, the methods of statistical analysis and hence the conclusions.

1.1. RETROSPECTIVE STUDIES

As brain tumours are relatively rare, the majority of studies are retrospective. Such ex post facto studies, are frequently referred to as correlational studies (Brink, 1990). In this type of research there is no manipulation of the independent variables because the event of interest has already occurred. The purpose of this type of design therefore is to describe existing relationships between the variables and to determine the relationship between independent and dependent variables. Where there is a correlation, a change in one variable corresponds with a change in another variable. However the presence of a correlation does not indicate causation. According to Christensen (1994), a correlational approach

measures the variables in their natural state as the variables are not manipulated. If a reliable relationship is found between two variables, then not only can the relationship between the variables be described but one variable can be predicted through knowing the other.

Advantages of retrospective designs are that: they are cost-effective and time-efficient, they utilize large samples from a given population, they may be the only feasible approach to studying rare diseases, such as paediatric brain tumours and they provide meaningful information about the way variables function in relation to one another.

However a major disadvantage is the problem of backward contingency probabilities. Huge advances in science and technology can skew results.

"the selected sample of the subjects is an unknown proportion of the affected population and therefore does not represent the true frequency of such individuals in the population."

(Gottfried 1973, in Spreen, 1995 p, 177).

Other potential sources of bias are incomplete or inaccurate historical records, attrition and selection bias.

1.2. OBJECTIVES OF STUDY

Neuropsychological assessment is part of an Oncology Clinic Programme for children with brain tumours being treated at Red Cross War Memorial and Groote Schuur Hospitals in Cape Town, South Africa. The present research attempts to identify which children are at risk following treatment for paediatric posterior fossa brain tumours, understanding the types of risk they face and creating a climate in which they can optimize their quality of life.

The two aims of the study are:

- to describe the neuropsychological sequelae and quality of life of posterior fossa brain tumour survivors treated by means of surgery, radiotherapy and chemotherapy.

- to examine the relationship between the independent variables and dependent outcome variables measured by a neuropsychological test battery and quality of life instruments.

The independent variables are:

- Age-at-Diagnosis, Age-at-Testing, Years-since-Treatment
- socio economic status, demographics and psychosocial disadvantage
- tumour type – astrocytoma, medulloblastoma, ependymoma and brain stem glioma
- pretreatment factors
- treatment, - surgery, shunt revisions, radiotherapy and chemotherapy.
- selected post treatment complications – transient cerebellar mutism, growth hormone deficiency and seizures

The dependent variables are:

- the neuropsychological test scores in the domains of attention, motor functions, speech and language, visual perceptual information processing, memory and intelligence
- emotional and behavioural test scores
- health-related quality of life test scores

This is a unique study in that it is the first of its kind to be undertaken at South African hospitals. Quality of life in the context of outcomes for brain tumour survivors is measured by a battery of neuropsychological, emotional, behavioural and health tests.

In the subsequent chapters the medical and surgical findings pertinent to the topic are given, followed by the neuropsychological and quality of life outcomes. Chapter 2 describes the problems associated with both the classification and incidence of posterior fossa brain tumours. A literature review of the pretreatment factors appears in Chapter 3, followed by a survey of the treatment factors of surgery, radiotherapy and chemotherapy in Chapter 4. Selected complications following treatment are discussed in Chapter 5, while Chapter 6 reviews the neuropsychological and quality of life outcomes in brain tumours. Appendix H cites all the studies discussed in Chapter 6. The method of the research and the results are in Chapter 7. Appendix A tabulates a description of the Groups and the treatment related variables. The neuropsychological test results are in Chapter 8, quality of life results are in Chapter 9, age-at-diagnosis and time-since-treatment findings are in Chapter 10. Chapter 11 covers medulloblastoma tumours. The model predictive of outcome is described in Chapter 12. The discussion, conclusions and recommendations for future research are to be found in the final Chapter 13.

CHAPTER 2

TUMOURS OF THE POSTERIOR FOSSA OF THE BRAIN

2.1. INTRODUCTION

Approximately half the number of all childhood brain tumours arise in the posterior fossa (Packer, Schut, Sutton *et al.,* 1990), which is the largest and deepest of the three cranial fossae. This area is bounded anteriorally by the dorsum sellae, the posterior aspect of the body of the spenoid bone, and the basilar aspect of the occipital bone. Inferiorally, the posterior fossa is bordered by the occipital bone and laterally by portions of the temporal, occipital, and parietal bones. Superiorally, the contents of the posterior fossa are enclosed by the tentorium cerebelli. This portion of the dura mater covers the cerebellum and supports the occipital lobes. The cerebellum and the inferior aspect of the brainstem are contained within the posterior fossa (Halperin *et al.,* 1994).

The majority of paediatric brain tumours occur below the tentorium (infratentorial) and 40 percent of these are embryonal in type (mainly medulloblastomas). In adults, most tumours occur above the tentorium (supratentorial) and are commonly astrocytomas or secondary tumours (Poldenak & Flannery, 1995).

2.2 CLASSIFICATION

The lack of a uniformly accepted classification system has been a major stumbling block in the evaluation of both the incidence of types of posterior fossa brain tumours and of the impact of treatment on children with brain tumours (D'Anglio, Rorke, Packer *et al.,* 1990; Miller, Young, Novakovic *et al.,* 1995).

Classifying cancer by anatomic site, reveals not only the frequency of one form of cancer, but the combined frequency of diverse cancers of that site. Among the childhood cancers, classified according to anatomical axis, leukaemia (31.4%) has the highest frequency, followed by a 17.6% frequency for malignant brain and CNS neoplasms (Miller *et al.,* 1995).

Rorke, Gilles, Davis *et al.,* (1985) recommend that all childhood brain tumours composed of primitive or undifferentiated cells be called primitive neuroectodermal tumours (PNET). Within the category of PNET are childhood brain tumours in different regions of the neuraxis which have been identified by a variety of names, including medulloblastoma and ependymoblastoma. The 1993 World Health Organization (WHO) classification of CNS neoplasms includes medulloblastoma as one of the paediatric embryonal tumours, identified as a specific PNET arising in the posterior fossa (Kleinhues, 1993). In this study, cognisance has been taken of this and the histological diagnosis is included in a description of the groups (see Appendix A).

2.3. TUMOUR TYPE AND INCIDENCE

The most common childhood tumours of the posterior fossa are medulloblastoma, low-grade cerebellar astrocytoma, brain stem tumours and ependymoma (Halperin *et al.,* 1994).

Table 2-1 *Posterior Fossa Tumours of Childhood*

TUMOUR	PERCENT
Medulloblastoma	30-40
Cerebellar Astrocytoma	25-35
Ependymoma	5-10
Unbiopsied Brainstem Glioma	5-20
Other	1-10

Source; Halperin *et al.,* (1994) p 91

2.3.1 Medulloblastoma

Medulloblastomas are primitive neuroectodermal tumours occurring in the posterior fossa, predominately in children. They arise in the cerebellar vermis and usually extend into the fourth ventricle and can spread through the CSF pathways, seeding into the lateral ventricles or spinal theca (Lindsay, Bone & Callander, 1991).

Medulloblastoma was first categorized in 1925 as a malignant neoplasm of the cerebellar region by Bailey and Cushing in their classification of CNS tumours (Cushing, 1930). Medulloblastoma is the most common childhood brain tumour occurring in the posterior fossa (Bloom, Glees & Bell 1990; Danjoux, Jenkin, McLaughlin *et al.,* 1996). As shown in the above table, the incidence ranges between 30 – 40% (Halperin *et al.*, 1994)

A retrospective population-based study carried out in Avon, U.K. from 1976 to 1991, indicated a significant decline in the incidence rates for medulloblastoma in children, from 9.6 to 1.7 per million per year (Thorne Parson, Nicoll *et al.,* 1994). This decline was not found in other types of posterior fossa tumours.

Certain diagnostic terms have been used to describe the histological variations of medulloblastoma (Sutton *et al.,* 1989).

- Rorke (1983) proposes that all such tumours composed of undifferentiated neuroepithelial cells be considered as a group and labelled primitive neuroectodermal tumours (PNET). This system further subclassifies PNET on the basis of the presence or absence of cellular differentiation along neuronal, glial or ependymal lines.

- Sutton *et al.,* (1989) classifies medulloblastomas as undifferentiated and multidifferentiated as they believe the degree of differentiation to be an important predictor of outcome. In their study, 15/23 children with differentiated tumours relapsed compared with only 4/20 with undifferentiated tumours. However, Caputy (1987) in Sutton *et al.,* (1989), discovered the opposite, showing that degree of cellular differentiation was predictive of improved outcome.

- According to Packer (1999) approximately 30% of children with medulloblastoma tumours will have disseminated disease at the time of diagnosis. Prospective randomized trails performed in the 1970's and early 1980's showed that staging studies were useful in stratifying children with medulloblastoma tumours into "average risk" and "poor risk" according to the dissemination of the tumour, extent of the surgical resection and involvement of the brain stem. With improved technology, the advent of the MRI and time there has been a reassessment of risk factors in determining the treatment protocols of radiotherapy and chemotherapy for children with medulloblastoma tumours. These are given in the table below.

Table 2-2 *Stratification of Medulloblastoma Tumours*

	Poor risk (any factor)	**Average risk**
Extent of disease at diagnosis	Disseminated	Localized
Extent of primary disease after surgery	Lump disease (especially after biopsy only)	Minimal or no residual disease
Age at diagnosis	Less than 3 years	3 years or greater

Source Packer *et al.*, (1999) page 77.

The histological variations in medulloblastoma are a cause of confusion in predicting outcome as well as the reassessment of the risk factors which have occurred over time.

2.3.2 Brain Stem Tumours

The management of brainstem glioma, is an area of controversy (Hoffman & Goumnerova, 1991).

Brain stem tumours represent 10% to 15% of all intracranial childhood neoplasms (Packer, Nicholson, Venzina *et al.,* 1992 in Kaplan, Albright, Zimmerman *et al.,* 1996). At the same time, the incidence of unbiopsied brain stem gliomas of the posterior fossa tumours in childhood is 5% to 20% (Cohen & Duffner 1984; Undjian, Marinov & Georgiev, 1989).

However, some studies cite slightly higher incidence rates of 10% to 20% or 25% (Hoffman & Goumnerova 1991), whereas other reports suggest that brain stem tumours occur as frequently as medulloblastomas and astrocytomas (Stroink, Hoffman, Hendrick *et al.,* 1987).

In 1969, Matson stated that "regardless of specific histology, brain stem gliomas must be classified as malignant tumours as their location itself renders them inoperable" (Matson, 1969 in Hoffman & Goumnerova, 1991, p326).

The number of classification systems of brain stem tumours may lead to confusion not only in the literature but in calculating the incidence.

- Epstein classified brain stem tumours radiographically into four types: diffuse, focal, cystic and cervicomedullary (Epstein & Wisoff, 1989, in Halperin *et al.,* 1994).

- A fifth category of brain stem glioma, the tectal gliomas, was added (Molloy, Sutton, Yachnis *et al.,* 1995).

- A staging system based on computerised tomography (CT) criteria of tumour location and characteristics; such as intrinsic versus extrinsic tumour, solid versus cystic components and contrast enhancement has also been described (Stroink, Hoffman, Hendrick *et al.,* 1987).

- Another difficulty is that surgical biopsy is often not performed because of the morbidity associated with the procedure, or the inconclusive pathological report (Molloy *et al.,* 1995).

In the Surveillance, Epidemiology and End Result (SEER) programme (1973 –1987), of 1642 brain tumours with a confirmed diagnosis, 198 cases of gliomas were excluded from the series because the diagnosis was made without histological confirmation, due to the inaccessibility of the tumour for a biopsy (Miller *et al.,* 1995).

Diagnosis normally depends upon procedures such as computerised tomography (CT) and magnetic resonance imaging (MRI). As the quality of radiology has improved over the last 10 years, lesions are now detected at an earlier stage, with a concomitant variation in the incidence of the tumours (Molloy *et al.,* 1995).

2.3.3 Cerebellar Astrocytoma

Cerebellar astrocytomas are low grade, well-circumscribed slow-growing lesions. Two thirds of these are cystic and in them the tumour is present as a mural nodule in 40%, with the remaining cyst wall being compressed cerebellar tissue. In the remaining 60%, the entire cyst wall is lined by tumour (Kernohan & Sayre, 1952; Russell & Rubinstein, 1971 in Halperin *et al.,* 1994). Initially Cushing (1931, in Halperin *et al.,* 1994) did not recognize that the mural nodule represented the malignant portion of many cerebellar astrocytomas. Without removal of it, the cyst was likely to recur, but once the nodule was recognized and removed by surgery, results improved.

In a review by Halperin *et al.,* (1994) cerebellar astrocytomas constituted 25% to 35% percent of all childhood posterior fossa brain tumours.

- The frequency of childhood cancer by histologic type according to SEER 1973 – 1987, reveals that astrocytoma is the second most common childhood cancer type after ALL and occurs at an incidental rate of 9.6% (Miller *et al.,* 1995).

- In considering the incidence of specific histologic types within the CNS, that of astrocytomas according to SEER 1973 – 1987 is 54.3% (Miller *et al.,* 1995). The incidence rates can then be subdivided in terms of confirmed histologic astrocytoma type.

- According to Gurney in Morris, Krawiecki, Kullgren *et al.,* (2000) European American children have incidence rates 22% higher than those of African American children. Incidence rates in South Africa may thus be lower for African children in South Africa compared to those of European extraction.

- Astrocytomas are described histologically as anaplastic and benign types. The benign types can be further subdivided into low-grade tumours of the fibrillary, juvenile pilocystic or diffuse types (Lindsay, Bone & Callender 1991).

2.3.4 Ependymoma

Ependymomas may arise from the ependymal lining of the floor, lateral recess, or roof of the fourth ventricle, third ventricle or lateral ventricles (Halperin *et al.,* 1994).

The incidence of ependymoma in all childhood cancer types according to histology, in the SEER 1973-1987 classification is, 1.7% (Miller *et al.,* 1995).

The incidence of ependymoma according to histologic types of CNS in children age 0 to 14 years of age, in the SEER 1973 – 1987 classification is 9.9% (Miller *et al.,* 1995).

Intracranial ependymomas, including supratentorial and infratentorial sites represent 1%–3% of all intracranial tumours in all age groups and 10% of intracranial tumours in children (Vanuytsel, Bessel, Ashley *et al.,* 1992).

The incidence of ependymomas among childhood tumours of the posterior fossa is 6%–12% (Bouffet, Perilongo, Canete *et al.,* 1998).

Incidence rates are confused, due to the lack of specification between infratentorial and supratentorial ependymomas and the different classification systems.

The histological subtypes are:

- Predominantly cellular, predominantly fibrillary, mixed cellular and papillary groups (Bailey, 1948; Healey, Braners, Kupsky *et al.,* 1991; Salazar, Castro-Vita, VanHoutte *et al.,* 1983; Schiffer, Chio, Girodana *et al.,* 1991, all cited in Haplerin *et al.,* 1994).

- Ependymomas may also be classified as Grade I, II, III, or IV based on the degree of anaplasia, cellular pleomorphism and necrosis (Kernohan & Sayre, 1952; Ringertz & Reymond, 1949; Russell & Rubinstein, 1971; Salazar *et al.,* 1983, all cited in Halperin *et al.,* 1994).

- Most pathologists prefer to group the cases as low grade or high grade (Halperin *et al.,* 1994). Other pathologists may prefer to classify them as ependymoma (equivalent to "low grade" ependymoma or "benign" ependymoma), anaplastic ependymoma or the rare embryonal tumour ependymoblastoma (Goldwein, Leahy, Packer *et al.,* 1990).

2.4 INCIDENCE RATES OF CANCER IN SOUTH AFRICA 1990-1991

In all histologically diagnosed cancer, the incidence of brain cancer, among all age groups, for females is 0.529% and for males is 0.608% (South African National Cancer Registery Report, 1990 – 1991).

Table 2-3 *Age specific cancer rates per 100 000, 1990 – 1991, South Africa*

FEMALE				
Age Yrs	0-4	5-9	10-14	15-19
Brain	0.47	0.577	0.748	0.511

MALE				
Age Yrs	0-4	5-9	10-14	15-19
Brain	0.664	0.736	0.692	0.354

Brain cancer in children is rare as indicated by the South African rates, there being little difference shown in the female and male incidence rates. At the time of writing this thesis, these were the only figures available.

2.5. SURVIVAL

Mortality in the general population is low among children, and there is little difference in survival rates with different conditions. Thus almost one in four children with cancer has an 80% or better chance of surviving for five years (Miller *et al.*, 1995).

The trend in relative survival rates for the most common histological types of childhood cancers for 1973-1987 is shown below. The number of cases in each category for both sexes and all races combined over this period ranges from 120 to 753. Little change in survival rate is shown in any of the main forms of brain cancer. Patients with astrocytomas had the best survival (approximately 70%) followed by those with medulloblastoma and ependymoma.

Table 2-4 *Five-Year Relative Survival Rates for the Most Common Histologic Types of Cancer Among Children Age 0 – 14, All Races, Both Sexes, SEER 1983-87*

DIAGNOSTIC GROUP	1973-77 (%)	1978-82 (%)	1983-87 (%)
Brain, CNS and Intracranial Neoplasms			
Ependymoma	33.7	28.7	46.5
Astrocytoma	65.3	71.0	71.1
Medulloblastoma	41.1	51.5	47.9*
Other Glioma	44.9*	43.8*	56.9*

SEER : Surveillance, Epidemiology and End Results

- : Standard error > 5% and 10%

2.5.1 Medulloblastoma

During the past 30 years, radical surgical removal of the medulloblastoma brain tumour, followed by radiotherapy to the craniospinal axis, with or without complementary chemotherapy, has been responsible for an improvement in the five-year survival rate to 50% or better for these tumours (David, Casey, Haywood *et al.,* 1997; Jenkin, 1996; Packer, Sutton, Elterman *et al.,* 1994).

2.5.2 Brain Stem Tumours

Brain stem tumours were once regarded as a universally fatal disorder but, depending on the specific type, the amenability to surgery, improved radiotherapy and chemotherapy regimes, the prognosis has improved (Hoffman & Goumnerova, 1991; Mulhern, Heideman, Khatib *et al.,* 1994).

A paediatric oncology group study, with 136 patients aged between three and 21 years, with tumours arising in the midbrain, pons or medulla, were treated with radiotherapy delivered to local fields. The results were poor;

the median survival time was ten months; survival at one year was 39.9% and at two years, seven percent (Freeman, Krischer, Sanford *et al.,* 1993).

A study was carried out in France between 1970 and 1990 on 75 children, who had intrinsic (3 cases) and exophytic (72 cases) brain stem tumours. The goal of surgery was to remove as much tumour as possible (Pierre-Kahn, Hirsch, Vinchon *et al.,* 1993). The study supports the hypothesis that surgical removal of brain stem tumours is only beneficial to children with benign tumours in which long term survival is the rule (Epstein & Wisoff, 1987; Hoffman, Becker & Craven, 1980; Littman, Jarrett, Bilaniuk, *et al.,* 1980; Stroink *et al.,* 1987). In this study surgery does not improve the prognosis of malignant tumours and survival time rarely exceeds 18 months (Pierre-Kahn *et al.,* 1993).

2.5.3 Cerebellar Astrocytoma

The survival rate of low-grade gliomas, (pilocytic astrocytomas, nonpilocytic fibrillary and protoplasmic astrocytomas, low grade oligoastrocytomas and oligodendrogliomas) has been reported to be 95% at 5 years, 93% at 10 years and 85% at 20 years (Pollack, Claasen, Al-Shboul *et al.,* 1995). On the other hand a cure rate of 80% to 100 % for patients treated for grade 1 and grade 11 cerebellar astrocytomas is reported at the Mayo Clinic (Morreale, Ebersold, Quast *et al.,* 1997). High-grade cerebellar astrocytomas in children are rare, survival is poor and dependent on individual treatment regimes (Campbell, Pollack, Martinez *et al.,* 1996).

2.5.4 Ependymoma

The survival rates of posterior fossa ependymoma are difficult to interpret because most series do not distinguish tumour location in their evaluations, although it has been reported that biological activity is related to tumour location. Contrary to expectations Needle, Goldwein, Grass *et al.,* (1997) found treatment failure occurred in patients with posterior fossa tumours

whereas others claimed that supratentorial tumours were a poor prognostic factor. Survival rates are further confused by the addition of single institution reports as opposed to large national or international studies, which could provide enough information for multivariate analysis of prognostic factors (Bouffet *et al.,* 1998).

In a literature review of posterior fossa ependymomas from the Mayo Clinic, confounding factors are highlighted (Lyons & Kelly, 1991)

1. The journal articles span several decades and do not take note of changes in treatment options.
2. They include patients with pre-existing metastases.
3. They do not report the degree of tumour resection.
4. They interpret the grading systems differently.

Consequently the five year survival rate ranges from 11% to 80% (Chin, Maruyama Markesbery *et al.,* 1982; Ernestus, Wilke & Schroder, 1989; Garrett and Simpson, 1983; Goldwein, Leahy, Packer *et al., 1990;* Salazar, Castro-Vita, Van Houtte *et al.,* 1983; Shaw, Evans Schethauer *et al.,* 1987). At the same time the five year survival rate for children in the Mayo Clinic series was 14% (Lyons & Kelly 1991).

2.6. EXPLORATION OF TUMOUR SITE AND TYPE TO NEURO-PSYCHOLOGICAL AND QUALITY OF LIFE OUTCOMES

One of the most challenging tasks facing the investigation of the effects of treatment on survivors of posterior fossa tumours is the heterogeneity of the disease in regard to tumour site and the type of tumour. It is typical for samples to include various types of tumours located in diverse regions of the brain. Of the sixty three studies reviewed (See Appendix H) 21% (13) studies used posterior fossa site of tumour and different types of posterior fossa tumours within the sample as the main organizing variables to demonstrate the effects of treatment on outcome (Chapman *et al.,* 1995;

Duffner, Cohen, Anderson *et al.,* 1983; Grill, Kieffer-Renaux, Bultea *et al.,* 1999; Hetherington, Dennis P Spiegler, *et al.,* 2000; Hirsch, Renier, Czernichow *et al.,* 1979; Hoppe-Hirsch *et al.,* 1995; Le Baron, Zelter, Zelter *et al.,*1988; Mulhern, Reddick, Palmer *et al.,* 1999; Packer *et al.,* 1989; Radcliffe *et al.,* 1992; Riva, Pantaleoni, Milani *et al.,* 1989; Seaver *et al.,* 1994; Sutton *et al.,* 1989).

2.6.1 Classification Of Paediatric Brain Tumours

Understanding the literature on paediatric brain tumours requires a familiarity with the current nomenclature as well as the historical development of these systems. As shown in the review, authors moved between old terminology such as glioma or non glioma tumours (Onoyama, Mitsuyuki, Takahashi *et al.,* 1975) to primitive neuroectodermal tumours when referring to medulloblastoma (Packer *et al.,* 1987; Packer *et al.,* 1989). Others differentiated medulloblastoma and primitive neuroectodremal tumours (Moore *et al.,* 1992) whereas some researches categorized them together (Packer *et al.,* 1987; Packer *et al.,* 1989).

The classification of astrocytoma brain tumours is also confusing. Most authors referred to cerebellar astrocytomas when describing astrocytomas which are sited in the posterior fossa brain region. However, some authors graded the astrocytoma tumours as type 1 or type 2 (Moore *et al.,* 1992) or used terminology such as dorsally exophytic /juvenile pilocytic astrocytoma and fibrillary astrocytoma (Mulhern *et al.,* 1994) or low grade astrocytoma (Chadderton *et al.,* 1995).

These different interpretations of the classification of posterior fossa brain tumours could possibly confound the results when comparing studies by different authors over a long time span.

2.6.2 Tumour Site and the Cerebellum

The contribution of tumour site to intellectual outcome is a debatable issue in resolving the impact of treatment on paediatric posterior fossa tumours, especially as the role of the cerebellum in cognition has recently come to the fore. The traditional view of the cerebellum is that it coordinates gait and voluntary movement, is responsible for balance and posture, and is important in speech and control of gaze (Schmahmann, 1997). However a more recent theory is that the role of the cerebellum is not limited to motor control, although this view has not gained wide acceptance. Neuroimaging studies (Parsons & Fox in Schmahmann, 1997) report cerebellar activation in support of such cognitive processes as semantic association, attention, working memory, verbal learning and memory. Neuroimaging studies also indicate that vermal cerebellar activation is associated with emotional states such as panic, sadness, depression and fear. It is likely that these mental conditions have few or no motor components but possess various sensory and cognitive components. A double dissociation between (a) cerebellar activity and sensory processing and (b) motor behaviour and activity in known motor areas in the cerebral cortex, is proposed by Parsons & Fox in Schmahmann (1997).

2.6.3 Neuropsychological Functioning and Quality of Life Related to Tumour Site

Many authors used supratentorial versus infratentorial site as a basis for comparison to predict cognitive and quality of life outcome (Cohen, Packer Siegel *et al.,* 1993; Duffner, Cohen & Parker, 1988; Horowitz, Mulhern, Kun *et al.,* 1988; Jannoun & Bloom, 1990; Kun *et al.,* 1983; Lannering *et al.,* 1990; Mulhern and Kun, 1985).

A greater than normal risk for late neuropsychological alterations among children with supratentorial tumours and/or cranial irradiation as opposed to infratentorial and/or cranial irradiation is described by Kun *et al.,* (1983),

who found that children with posterior fossa tumours had no intellectual impairment at diagnosis. However, abnormal social emotional functioning was recorded in a greater number of children with supratentorial tumours than posterior fossa tumours after surgery and radiotherapy treatment. The small sample size limits the interpretation of the results. According to Mulhern and Kun (1985), there was no consistent influence of tumour site on selective attention, intellectual functioning or emotional adjustment except for younger patients. The children younger than six years at diagnosis with supratentorial tumours were less likely to improve their cognitive performance than the infratentorial group.

Ellenberg *et al.,* (1987) demonstrated that tumour site is critical to the degree and nature of functional sequelae in children with brain tumours. The deficits observed in children with hemispheric tumours are similar to those of adults and support notions of early lateralization in human development. The patients also showed general intellectual deficits that predated the diagnosis. The global dysfunction was hypothesized as being due to interference by the tumour with surrounding brain tissue. Children with lesions of the anterior third ventricle, craniopharyngioma or hypothalamic tumours were more likely to be severely impaired. They, like adults with third ventricle tumours, showed prolonged periods of lowered consciousness, amnesia or confused thinking that lasted up to four months after the operation.

As IQ data was collected prospectively, over time it was possible to examine IQ changes by using each subject as their own control. Children with hemispheric tumours showed much lower IQ scores at all testing points than those with third or fourth ventricle tumours. Patients with third ventricle tumours maintained their IQ levels from four months post diagnosis over the one to four years of the study whereas subjects with fourth ventricle tumours showed a significant drop in IQ from four months to between two to four years post diagnosis. The downward trend was also found in patients with hemispheric tumours, but, because of small numbers,

the trend did not reach a significant level. The decline in IQ over time for patients with fourth ventricle tumours was attributed to RT rather than tumour site.

By controlling for tumour type and site and using a variety of neuropsychological tests, Brookshire, Copeland, Moore *et al.,* (1990) identified the relationship between tumour-related factors and specific neuropsychological abilities. Tumour site and symptom duration correlated with the executive domain score, indicating that patients with cerebral hemisphere tumours and a longer duration of symptoms performed less well on executive measures. Seventy one percent of the cerebral hemisphere, 64% of the supratentorial midline and 73% of the infratentorial tumour groups performed within or above the normal limits on all neuropsychological tests except the executive domain. A significant correlation between cerebellar signs and visual motor and fine motor domain scores indicated a strong relationship amongst these indices of motor function. The authors note that the association between cerebellar deficits and fine motor and visual motor domains is an expected finding since the cerebellum is associated with motor functions. The results of the study also showed that as a group, children with primary brain tumours are not intellectually impaired before treatment.

The most important factors underlying moderate to severe disabilities in long term survivors of paediatric brain tumours are the presence of supratentorial tumours and cranial irradiation. According to Jannoun and Bloom (1990), intellectual differences were not found between infratentorial and supratentorial tumours but quality of life indices were better in the infratentorial group. The Bloom Functional Disability Scale showed that 72% of patients with supratentorial tumours had mild to severe neurological and physical disability compared with 44% in the infratentorial group.

Lannering *et al.,* (1990) compared the functioning of subjects with supratentorial and infratentorial tumours, treated by means of surgery only.

No significant differences were found in intellectual scores, motor dysfunction, visual dysfunction, or short stature. Subjects with supratentorial tumours had significant psychological and emotional difficulties and moderate to severe disability impairment profiles, compared with those with infratentorial tumours. Motor impairment was expressed according to tumour site. Hemisyndromes in supratentorial tumours generally caused little disability whereas truncal ataxia in infratentorial tumours caused moderate to severe disability and had confined two patients to wheelchairs. Despite normal findings on gross neurological examination, Stott's test reveals moderate to significant problems in 45% of all the subjects which was significantly more than expected in the normal population. For supratentorial tumours the dysfunction affected manual dexterity, eye and hand coordination and balance. However, for infratentorial tumours the dominant finding was in disturbed balance.

Tumour site and treatment were associated with changed quality of life measures in the studies by Mostow *et al.,* (1991). Survivors of supratentorial tumours and those who received radiation treatment were at greater risk of adverse outcomes than survivors of infratentorial tumours who had not received radiation. The findings were verified by using sibling controls. The greatest difference between supratentorial and infratentorial tumours was in emotional problems and mental incompetence. These findings are based on a large retrospective sample (342 subjects and 479 sibling controls) over a 29 year period.

The association between brain tumour site and memory functions is reported in a series of publications (Dennis, Spiegler, Fitz *et al.,* 1991; Dennis, Spiegler, Hoffman *et al.,* 1991; Dennis, Spiegler, Obonsawin *et al.,* 1992). A complex tabulation of brain tumours by means of both focal site and invasion of the tumour into other regions was completed, based on CT scans. Subjects could have more than one entry to account for both the focal and the invasive areas of the tumour. The diencephalon and the cerebellum were the most common tumour sites. The sample of 46

paediatric brain tumours comprised 23 craniopharyngiomas (50%) localized in the diencephalon and six medulloblastomas (13%) which were in the cerebellum. Tumours such as astrocytomas (17%), germinomas (7%), other cysts (7%), neuroectodermal (2%) lipoma (2%) had multiple entries in various parts of the brain.

The working memory tasks were unaffected by demographic and medical variables, although the memory for serial order of pictures that corresponds with the heard word was inversely related to Age-at-Diagnosis. Notwithstanding the demonstrated importance of anatomical locus of the tumour, Dennis highlights the fact that a considerable variance in the memory score remains unaccounted for, showing that factors other than anatomical sites of damage contribute to memory deficits in brain tumour subjects.

Working memory in a sample of craniopharyngioma, anterior third ventricle, posterior third ventricle and fourth ventricle tumours showed no effect for tumour site (Dennis, Hetherington and Spiegler, 1998). The authors suggest that tumour site in future studies should be analysed on the basis of neuroimaging studies to include tumour damage, as well as location of the primary tumour.

Tumours that involve the hypothalamus and/or optic chiasm have been directly related to decline in IQ and memory functioning (Danoff, Cowchock, Marquette *et al.,* 1982 in Mulhern and Kun, 1985).

Two prospective studies (Packer *et al.,* 1989; Sutton *et al.,* 1989) that used serial testing showed that the site of the tumour is an important determinant on cognitive outcome. Both these studies found that at baseline testing after surgical intervention, the cerebellar astrocytoma group and the medulloblastoma group, had fine motor speed and dexterity impairments. In the cerebellar astrocytoma group that had no further treatment, no

improvement in these functions was found two years later. The deficits were thus attributed to the site of the tumour.

Of the studies reviewed only one study discussed astrocytoma tumours located in various sites of the brain as the organizing variable to illustrate the effects of treatment outcome (Chadderton *et al.,* 1995). They found that the site of the tumour had little impact on intellectual functioning but that treatment related factors negatively affected cognitive functioning. Children treated by means of surgery only had relatively intact IQ scores whereas a decline in IQ scores was shown for those tumours sited in the posterior fossa area treated by means of Surgery and RT.

2.6.4 Neuropsychological and Quality of Life Outcomes related to Tumour Type.

The survival rates for different types of posterior fossa tumours indicate that cerebellar astrocytoma have the best prognosis, followed by medulloblastoma, ependymoma and lastly brain stem glioma tumours. Therefore, an important consideration in the interpretation of neuropsychological outcome is the differentiation between tumour types. Ris and Noll (1994) find in their review of paediatric brain tumours, that many authors had not taken this into account. They feel it is both a function of the rarity of many brain tumours as well as the controversy surrounding the classification of them.

Studies comparing the treatment outcome of children with malignant medulloblastoma tumours to children with low grade cerebellar astrocytoma tumours showed that the progression of the disease state and the biology of the type of tumour prescribed the type of treatment of surgery only or surgery RT and/ or chemotherapy (Grill *et al.,* 1999; Hetherington *et al.,* 2000; Hirsch *et al.,* 1979; LeBaron *et al.,* 1988; Mulhern *et al.,* 1999; Packer *et al.,* 1989; Riva *et al.,* 1989; Sutton *et al.,* 1989).

Studies comparing the performance of cerebellar astrocytoma tumours with other posterior fossa tumours, such as medulloblastoma tumours at baseline testing prior to treatment show that there is little difference between the cerebellar astrocytoma group and the medulloblastoma group in base line IQ test score results. Both these groups function within the normal range (Packer *et al.,* 1989; Sutton *et al.,* 1989).

However, at baseline testing Packer *et al.,* (1989) found that the medulloblastoma group had difficulties in fine motor function in motor speed and dexterity in both the dominant and non-dominant hand. Visual motor integration and visual spatial difficulties were only found in one or two subjects. Language difficulties were marginally evident, whereas memory difficulty was shown in more than half the sample. A similar pattern of difficulties was found in the astrocytoma group with the exception of memory, which was relatively well preserved and language difficulties in which two children were severely impaired. Small sample size (11) has a limiting influence on the generalizability of the results.

A retrospective comparison of low grade astrocytoma tumours in different sites showed that at baseline assessment there was no difference in the neurological function of all the tumour groups (Chadderton *et al.,* 1995). Later differences were attributed to treatment effects.

A unique study by Mulhern *et al.,* (1999) using a MRI protocol illustrated variations in the normal white matter and subsequent lower FSIQ induced by the caraniospinal radiation treatment of medulloblstoma tumours with or without chemotherapy. This result was not evident in the low grade astrocytoma tumours, all of which were sited in the posterior fossa. These results suggest that tumour site is not a contributing factor to these results. However the use of only FSIQ test scores is a limiting factor. A more extensive test battery may have illustrated deficits in other domains, such as visual perceptual information processing, thus highlighting the possible effect of the site of the tumour.

Hetherington *et al.,* (2000) demonstrated that childhood lesions of the cerebellum produced enduring deficits in short term duration perception, but spared the ability to functionally estimate duration, regardless of pathology or treatment. Evidence did not support any functional recovery over time of the cerebellar system that underlies short duration perception. A control group matched for age was used by the authors to verify their findings.

In the literature reviewed (Appendix H) three studies used ependymoma and medulloblastoma brain tumours as the organizing variables (Grill *et al.,* 1999; Hoppe-Hirsch *et al.,* 1995; Seaver *et al.,* 1994). Both these tumour types were treated with surgery, radiotherapy and to some extent chemotherapy. The study of Seaver *et al.,* (1994) was limited by small number of subjects. However the authors state that they specifically chose survivors of ependymoma and medulloblastoma brain tumours as both tumours are located in the posterior fossa and received similar types of radiation protocols. Tumour type was thus not considered a potential confound.

Hoppe-Hirsch *et al.,* (1995) found that ten years after treatment the FSIQ scores of the subjects with ependymoma tumours remained stable whereas FSIQ scores of the subjects treated for medulloblastoma brain tumours deteriorated. The same pattern was evident for school performance and behaviour. The authors concluded that progressive deterioration in function was due to treatment factors and not the type of tumour.

Grill *et al.,* (1999) discussed that tumour type and the presence of metastasis or incomplete surgical resection strongly correlated with the radiation dose as stipulated in the treatment policies and was therefore associated with poorer intellectual outcome. High risk medulloblastoma patients had metastasis of the tumour or incomplete surgery. After 1989 all children with standard risk medulloblastoma received the same amount of RT. After adjusting for confounding factors cranio spinal radiation dose was

found to be the most implicated in low intellectual scores. However the authors concede that studies of children treated for medulloblastoma and ependymoma brain tumours treated without radiation may be the only way of discovering if the site of radiotherapy treatment is implicated in low neuropsychological test scores.

Twenty one percent (13) of the studies reviewed (Appendix H) used medulloblastoma tumours only as the organizing variable (Broadbent, Barnes & Wheeler, 1981; Chin & Maruyama, 1984; Dennis *et al.,* 1996; Gajjar, Mulhern Heideman *et al.,* 1994; Hoppe-Hirsch *et al.,* 1990; Hudson & Murdoch, 1992; Johnson *et al.,* 1994; Koa, Goldwein Shultz *et al.,* 1994; Kimmings *et al.,* 1995; Nishiyama *et al.,* 1994; Packer *et al.,* 1987; Silverman, Plakes, Talent *et al.,* 1984; Yang *et al.,* 1997).

Long term survivors of medulloblastoma tumours are at risk for significant sequelae, including tumour related and treatment related complications. A major gap in the understanding and management of children with medulloblastoma tumours is the lack of biological factors, which can be used to stratify patients.

The longitudinal study of Radcliffe *et al.,* (1992) showed that neither the progression of the medulloblatoma tumours nor the site of the tumour affected the outcome as measured by FSIQ scores. The authors measured the extent of the disease at the time of diagnosis. Radcliffe *et al.,* (1992) also found that children younger than seven years of age at diagnosis fared worse after treatment than older children This study is unfortunately limited by the attrition of the sample over the four year period of the study, small size of the sample at commencement of the study and a possible lack of infants or very young children in the sample to adequately verify the age effects.

Grill *et al.,* (1999) demonstrated that poor risk medulloblastoma subjects who had higher doses of RT treatment had lower FSIQ scores than children

with standard risk medulloblastoma tumours. Few studies take this factor into account. This may be due to the fact that over time there has been a reassessment of these risk factors. In addition prior to the availability of MRI, which has only been available at most centres for the past ten years, myelography was the most sensitive means to determine spinal dissemination. This procedure could only be performed after surgery as medulloblastoma tumours occur in the fourth ventricle and are associated with hydrocephalus and a possible risk of brain herniation if done prior to surgery. Cerebrospinal fluid cytology is also used to diagnose spinal metastasis as according to Packer (1999) about 20% of children with medulloblastoma tumours will have positive cerebrospinal fluid cytology despite not having evidence of radiographic disease dissemination. Thus over time, progress in technology and improved diagnostic skills have led to a reassessment of the risk factors associated with medulloblastoma brain tumours which few researchers have taken into account.

2.7. SUMMARY

- The controversy surrounding a uniformly accepted classification system reflects the complexity of the diseases and the differing perspectives of the authors when presenting the incidence of posterior fossa tumours, as well as the impact of treatment on children with brain tumours.

- Medulloblastoma is the most common childhood brain tumour, followed by low-grade cerebellar astrocytoma, brain stem tumours and ependymoma.

- Cerebellar astrocytoma tumours have the best survival with a cure rate of 80% to 100%. The survival rate of medulloblastoma tumours has improved to about 50%, or better due to treatment changes whereas the survival rates for ependymoma are difficult to interpret and range from 11% to 80%. Brain stem tumours have a poor survival rate but

depending upon the diagnosis and treatment the prognosis has improved.

- The different interpretations of the classification of posterior fossa brain tumours is a possible confounding factor when comparing studies on neuropsychological and quality of life outcomes over a long period of time.

- The contribution of tumour site to neuropsychological and quality of life functioning is critical to the degree and nature of sequelae. Results discussed are variable but generally supratentorial tumours have a poorer outcome than infratentorial tumours in terms of neuropsychological impairment. Specifically for infratentorial tumours, attention and memory functions do not appear to be affected, IQ scores are reported to be within normal range at baseline testing, as are emotional functions. Overall motor impairment in both supratentorial and infratentorial tumours, which is expressed differently according to tumour site needs further evaluation.

- According to Packer (1999) in almost every series to date, children with tumours that arise outside of the posterior fossa have fared less well than children with posterior fossa tumours. It is unclear if this is related to the treatment or is due to biological differences between tumours of similar histology in different sites of the nervous system.

- Tumour type is an important consideration in the neuropsychological outcome of posterior fossa tumours, which many researchers do not include in their reviews of paediatric brain tumour survivors. At baseline testing however both astrocytoma and medulloblastoma survivors have similar patterns of neuropsychological difficulties and FSIQ scores (Packer *et al.,* 1989; Sutton *et al.,* 1989). The treatment decisions are often based on the diagnosis of the tumour type and site and underpin the neuropsychological outcome.

- Studies comparing children with ependymoma tumours to children with medulloblastoma tumours found that tumour type is not a confounding variable in the interpretation of the neuropsychological test scores. Low scores were attributed to treatment related factors rather than tumour related factors.

- Few researchers have considered the extent of the disease of the medulloblastoma tumours or the risk factors as described by Packer (1999) either in the compilation of their samples or the in the interpretation of the cognitive or quality of life results. The longitudinal study of Radcliffe *et al.,* (1992) found that the progression of the medulloblastoma tumour did not affect the outcome of FSIQ scores. A later study by Grill *et al.,* (1999) showed that the diagnostic criteria of the brain tumour survivors (tumour type and extent of the disease) correlated with the RT and/or chemotherapy treatment and the subsequent cognitive outcome which was in turn related to the treatment.

CHAPTER 3

FACTORS ASSOCIATED WITH PRETREATMENT STATUS

3.1. PRESENTING SYMPTOMS

According to Ris and Noll (1994), the role of the type and duration of clinical phenomena, such as nausea, vomiting, cranial nerve impairment, mental status changes, motor impairment and subsequent cognitive morbidity has not been well documented for posterior fossa brain tumours. A study by Packer, Sposto, Atkins *et al.,* (1987) shows that a lowered PIQ score was significantly associated with altered mental status and oculomotor deficit at diagnosis in 24 long-term survivors of PNET (medulloblastoma) located in the posterior fossa. In addition, children with a shorter duration of presenting symptoms showed a trend towards a poorer PIQ score.

Brookshire *et al.,* (1990), tested 31 children one to three days prior to removal of primary brain tumours. They reported that patients with infratentorial tumours had presenting symptoms such as headache, nausea and vomiting for a briefer period than patients with supratentorial tumours, with 58% of the sample indicating that the symptoms lasted for no more than three months. Fifty percent of the patients with infratentorial tumours also had ocular nerve deficits, while 77% of the group had cerebellar signs. A significant correlation between cerebellar signs and visual motor and fine motor domain score was found. However the correlation between tumour location and symptom duration and executive domain was not significant for infratentorial tumours.

A perioperative summary score, which included the tumour extending to the vermis, obtundation at presentation, hydrocephalus at presentation,

surgical intervention and post operative complications, was calculated by Chapman *et al.,* (1995). They found a significant association between perioperative summary score and poor neuropsychological outcome in their sample of 15 long-term survivors of posterior fossa brain tumours.

It may be that the lack of literature concerning the relationship between presenting symptoms and neuropsychological outcome is due to the fact of the signs and symptoms of the presenting symptoms being enmeshed in the symptoms of hydrocephalus and raised intracranial pressure (ICP).

3.2. HYDROCEPHALUS

Hydrocephalus is an abnormal increase in the amount of cerebrospinal fluid within the ventricles of the brain which may be acquired at any age as a result of neoplasm, trauma or brain infection. Children with posterior fossa tumours are predisposed to hydrocephalus because of the proximity of the fourth ventricle and the CSF pathways (Kumar *et al.,* 1996).

3.3. RAISED INTRACRANIAL PRESSURE

Although the brain tumour itself causes symptoms and signs, the complicating secondary hydrocephalus is often responsible for the increased intracranial pressure (ICP), thus superimposing a clinical picture of "midline syndrome", described by Raimondi & Tomita (1981), as "an increase in ICP without lateralizing signs". Thus the child may be considered to have two distinctly different diseases, a tumour and hydrocephalus, which complicate one another and contribute to the complex picture of increasing ICP (Raimondi & Tomita, 1981). Some children will require a CNS diversion procedure, such as a ventriculo-peritoneal shunt or an extraventricular drain, at some time during the course of their illness (Culley, Berger, Shaw *et al.,* 1994). Some authors advocate the pre-operative placement of a permanent shunt prior to surgical resection of the tumour, suggesting that this decreases patient

morbidity and mortality following the tumour resection (Raimondi & Tomita, 1981). Others find that pre-operative shunts can expose children to unnecessary risks such as upward herniation and other complications of shunting (Kumar *et al.,* 1996; Lee, Wisoff, Abbott *et al.,* 1994).

David *et al.,* (1997) report that, in their sample of medulloblastoma tumour children, those who required early CSF drainage were in the younger age group, were male and had a significantly shorter survival time. They suggest that the failure of hydrocephalus to respond to the tumour removal corresponds with the severity of the disease.

3.3.1 Complications Of Shunts

Complications associated with cerebral shunts are shunt malfunction, upward cerebellar herniation, infection, tumour haemorrhage and abdominal complications (Raimondi & Tomita, 1981). An added problem, the risk of extraneural metastases via the placement of shunts, has been suggested by some authors (Hoffman, Hendrick & Humphreys, 1976; Jamjoom, Jamjoom, Sulaiman *et al.,* 1993) but contested by others (Berger, Baumeister, Geyer *et al.,* 1991; Raimondi and Tomita, 1981).

Preoperative external ventricular drainage and the use of corticosteriods as methods of controlling the symptoms of hydrocephalus and avoiding the placement of a permanent shunt, together with the associated complications, have been advocated by some authors. They suggest that the use of this approach results in the majority of children remaining shunt free after resection of the brain tumour (Dias, Albright, 1989; Rappaport & Shalit, 1989 in Culley *et al.,* 1994).

The management of hydrocephalus in children with posterior fossa tumours thus differs according to the policy of the institution and the presenting symptoms.

3.4. HYDROCEPHALUS AND NEUROPSYCHOLOGICAL FUNCTIONING

As hydrocephalus is a syndrome with heterogeneous etiologies, it is difficult to distinguish which signs and symptoms result from the underlying lesion and which are related to the hydrocephalus itself. The research on hydrocephalus in animal experiments and human biopsy material shows that tissue damage is limited to the periventicular white matter with no accompanying loss of neurons (Bangash, D'Souza, Barbosa in Ashbury, McKhann, McDonald, 1992).

Although the study by Fletcher, Bohan, Brandt *et al.,* (1992) on cerebral white matter and hydrocephalus was carried out on children with meningomyelocele, meningocele and aqueductal stenosis and normal subjects, their findings on white matter changes and the concomitant neuropsychological effects are of relevance:

- The corpus callosum in the meningomyelocele and aqueductal stenosis groups was smaller.

- The lateral ventricles were larger and the internal capsules were smaller in the hydrocephalic groups than the normal subjects.

- No difference in the size of the centra semiovale was found.

- Verbal and nonverbal measures correlated positively with the size of the corpus collosum and a higher correlation was shown for nonverbal measures.

- Nonverbal measures correlated with the size of the right, but not the left lateral ventricle and with areas around the right and left internal capsule.

- Verbal measures correlated with the size of the left, not the right lateral ventricle and the left but not the right internal capsule

In order to obtain these results, the researchers measured cerebral white matter structures and lateral ventricles of the MRI of the age-matched sample

The volume of each lateral ventricle and the cross sectional area of the corpus callosum and internal capsules were correlated with the measures of verbal and nonverbal skills. The authors conclude from the findings the importance of white matter structures in the development of nonverbal cognitive skills and that the integrity of the central system white matter in both hemispheres is important for the development of nonverbal skills. Although specific language and attention deficits were not found, an impairment in higher cortical functions (as often shown in association with the posterior parietal areas of the right hemisphere) was demonstrated. The authors suggest that the failure of the system to develop because of reduced interhemispheric communication supports the facilitatory model of the corpus collosum and current theories of hemispheric specialization as described by Rourke (1982; 1987).

Dennis, Fitz, Netley *et al.,* (1981) show in a study of 78 children diagnosed with hydrocephalus before the age of 12 months, all of whom had been shunted, showed that the children had an uneven growth of intelligence during childhood. This study however excludes children with brain tumours or other lateralized neurological signs. In this instance nonverbal intelligence developed less well than verbal. Dennis hypothesizes that it was neither the hydrocephalic condition nor the treatment but the developmental brain anomalies and symptoms to which the hydrocephalic children are prone (ocular abnormalities, motor deficits and seizures) that accounted for the deficits. Specifically impairments found in fine motor control resulted in difficulties on time-limited nonverbal tasks. Impaired tactile perceptual performance was also found. Analysis of

variance was not significant for any IQ measurement in relation to type or number of shunts inserted. The average number of shunt revisions in the sample was 4.41.

The relationship between language development and hydrocephalus is well documented by Dennis, Hendrick, Hoffman *et al.,* (1987). They studied the language development of 75 children diagnosed with hydrocephalus in the first year of life and compared the results with those of 50 control subjects. They found that both groups showed the same age increments in language performance but that, with increasing age, hydrocephalic children fell behind. Deficits were also found in word finding and higher levels of language related academic skills. As language and intelligence shared a common variance of only 18% to 39%, it was suggested that language tapped functions other than those involved in intelligence.

Thus from these studies, it is clear that hydrocephalus per se can produce neuropsychological sequelae.

3.5. RELATIONSHIP BETWEEN HYDROCEPHALUS AND NEUROPSYCHOLOGICAL FUNCTIONING IN CHILDREN WITH POSTERIOR FOSSA TUMOURS

Hydrocephalus is a significant complication of infratentorial brain tumours (Raimondi & Tomita, 1981). Nevertheless the relationship between hydrocephalus, posterior fossa brain tumours and the subsequent effect on neuropsychological functioning is not clear. Mulhern (1994) suggests that the effects of episodic and temporary increases in intracranial pressure are not well understood. According to Cochrane, Gustavsson, Poskitt *et al.,* (1994), 8% of the children with posterior fossa tumours in their study required post operative shunts. This is a much lower incidence than that reported by Lee *et al.,* (1994), who found that 40% of children

with medulloblastoma tumours required a permanent post- operative shunt.

The effects of hydrocephalus on cognitive recovery are contradictory. A prospective study by Ellenberg *et al.,* (1987) shows that acute hydrocephalus is a common clinical presentation of children with brain tumours. The mean FSIQ scores of children with and without hydrocephalus, and third and fourth ventricle tumours improved over a four-month recovery period while the FSIQ of those with hemispheric tumours did not. Gains made by the non- hydrocephalic and hydrocephalic groups on FSIQ test scores over a three month test period were of the same order (5.5 points).

The hydrocephalic children who required shunts were more likely to have a diagnosis of third ventricle tumours, whereas those not needing a shunt (in whom the hydrocephalus resolved after tumour resection) were more likely to have fourth ventricle tumours. Children who required shunts four months post diagnosis, were more likely to have a higher mean FSIQ than those who did not. The seven point gain in FSIQ score by the group requiring shunts was significant while the four-point FSIQ gain by the group not requiring shunts failed to reach significance. This therefore suggests that in children with the most severe hydrocephalus there is an initial depression of cognitive functioning beyond that produced by the craniotomy and hence more early recovery.

Jannoun and Bloom (1990) show that the difference in FSIQ scores did not reach statistical difference in children with primary intracranial tumours and hydrocephalus (n=40; FSIQ=89) compared with those with brain tumours without hydrocephalus (n=22; FSIQ=99). Children with hydrocephalus were twice as likely to have a FSIQ within the educationally subnormal range as those without hydrocephalus (28% versus 14%). The authors give no explanation to account for these results, instead reporting that hydrocephalus was a presenting symptom

at the time of diagnosis and that in seven patients a CSF shunt was inserted. As this is a retrospective study, it could be assumed that by the time the subjects were given the neuropsychological assessment (3-20 years post treatment), factors other than hydrocephalus contributed to the scores, as well as the uneven distribution of subjects within each group.

The requirement of shunt placement to relieve intracranial pressure is shown by Packer *et al.,* (1987) to have a negative effect on FSIQ scores. In a retrospective study of 43 children diagnosed with medulloblastoma tumours, they found that children who had a shunt placement had a lower FSIQ (73) than those not requiring a shunt (FSIQ = 99).

Medulloblastoma survivors with a shunt placement for hydrocephalus had higher FSIQ scores (FSIQ = 79 versus 68), compared with those who did without (Johnson *et al.,* 1994). Achievement in reading, spelling and maths indices were also better for the hydrocephalic-shunt-placement group. Reduced motor dexterity and speed were significantly associated with a shunt placement. The authors conclude that their findings warrant replication because of the relatively small sample size (n=13).

Repeated shunt revisions carry a risk in cognitive morbidity. Kao, *et al.,* (1994) describe a case of an 18 month old infant who developed brain herniation, obdundation and arrest. She was subsequently revived and underwent emergency ventricuoloperitoneal shunting. One week after the second surgery she had meningitis and the shunt became infected. She required a third revision of her shunt and ultimately experienced a IQ drop of more than 40 points. This prospective study found a significant correlation between adverse perioperative factors such as shunt infections and IQ deficits. The authors used a multiple logistic regression analysis to evaluate the significance of the independent contribution of the prognostic factors, that is perioperative factors, in predicting the outcome (FSIQ) on 28 children diagnosed with medulloblastoma brain tumours.

The effects of increased intracranial pressure (ICP) on cognitive functioning remain uncertain in the study by Kun *et al.,* (1983). In their prospective study of 30 children with primary brain tumours they found that raised ICP did not differentiate between those children who exhibited intellectual delays and those who did not. In the sample of 17 children who had shunting procedures secondary to raised ICP, only 5 children (29%) showed intellectual delays, whereas, of the 13 not requiring shunts, 5 children (39%) had intellectual delays. The authors conclude that the results need to be confirmed with larger numbers of patients longitudinally studied prior to and following treatment.

Raised ICP was shown by Mulhern and Kun (1985) to have no significant effect on changes in IQ test scores. Prospectively, they assessed a group of 26 children with primary brain tumours (11 posterior fossa tumours and 15 supratentorial tumours) and tested them at baseline and six months after irradiation. Mixed tumour types and an uneven number of children with and without shunts are potential sources of distortion in their results. The authors hypothesize that their study may not adequately represent the late sequelae of brain tumours and their treatment as these are only likely to be recognized about five years after treatment. The study therefore provides insight only into early functional changes.

No significant difference between the presence of hydrocephalus (FSIQ=83) and the absence of hydrocephalus (FSIQ=90) on intelligence test scores was found by Yang *et al.,* (1997). They assessed 19 children diagnosed with medulloblastoma tumours, in 12 of whom a shunting procedure was performed for raised ICP. Small sample size and the fact that the majority of the sample required a shunting procedure have the potential to bias the results.

3.6 SUMMARY

- The role of presenting symptoms and subsequent neuropsychological functioning has not been well documented for posterior fossa brain tumours.

- Children with posterior fossa tumours are predisposed to hydrocephalus because of the proximity of the tumour to the fourth ventricle and CNS pathways.

- The placement of a ventriculo-peritoneal shunt or extraventricular drain to relieve the symptoms of raised ICP differs according to the policy of the neurosurgeons.

- Between 8% and 40% of children with a posterior tumours will require a post-operative shunt. Repeated shunt revisions and perioperative complications have been found to be associated with a dramatic drop in FSIQ (Kao *et al.*, 1994).

- Changes in cerebral white matter due to hydrocephalus and concomitant neuropsychological functions indicate that the integrity of the CNS white matter in both cerebral hemispheres is important for the development of nonverbal skills. The developmental brain anomalies and symptoms to which hydrocephalic children are prone are hypothesized to account for uneven growth of intelligence during childhood with nonverbal intelligence developing less well than verbal (Dennis *et al.*, 1981). The relationship between hydrocephalus diagnosed in the first year of life and language development showed that with increasing age, hydrocephalic children lag behind (Dennis *et al.*, 1987).

- Contradictory neuropsychological results have been found with regard to hydrocephalus and shunt placements in posterior fossa brain

tumour children. Low FSIQ scores are reported by some researchers (Jannoun & Bloom, 1990; Packer *et al.,* 1987). Others (Mulhern & Kun 1985; Yang *et al.,* 1997) report no difference; whereas Johnson *et al.,* (1994) found higher FSIQ scores in those who had a shunt compared with those without shunts.

CHAPTER 4

TREATMENT

4.1. INTRODUCTION

Cushing's critical review (1930) of his inability to cure children of medulloblastoma brain tumours by means of surgical resection only, paved the way for a possibility of cure by means of post-operative irradiation. The modern goal of surgical resection in the treatment of posterior fossa tumours involves relief of obstructive symptoms by surgical decompression of the tumour and, when necessary, placement of a shunt as well as tumour removal (Halperin *et al.,* 1994).

Most literature on posterior fossa tumours and the role of surgical resection is concerned with survival. The evidence strongly suggests that a survival benefit accrues after the removal of as much tumour as possible, consistent with preservation of neurological function (Albright, Wisoff, Zeltzer *et al.,* 1996; Bloom *et al.,* 1990; Lyons & Kelly, 1991; Packer, Sutton, Goldwein *et al.,* 1991).

4.2. SURGICAL RESECTION OF BRAIN TUMOURS

Tumour type and the associated natural morbidity of the tumour are confounding variables when investigating the effects of the extent of surgical resection on outcome.

This is well illustrated in a study by Cochrane *et al.,* (1994) who investigated the surgical and natural morbidity of aggressive surgical resection of posterior fossa tumours in a sample of 102 children, all of whom underwent gross total resection. Thirty three of them suffered from intra and post-operative complications. Worsening of pre-operative deficit

occurred in 41% of the children operated on for medulloblastoma tumours, in 53% of ependymomas and 30% of astrocytomas. However complete recovery of the new post-operative deficits occurred within about six months in 14% of the medulloblastoma tumours, in 50% of the ependymoma and in 47% of the astrocytoma tumours. Residual neurological morbidity, due to the persistence of pre-operative symptoms or deficits incurred during the surgical procedure was not shown in 38% of the children, although 62% of the children continued to demonstrate abnormal cerebellar or bulbar signs. Limitation of function due to a residual deficit was shown in 43% of the subjects.

The variability of the results in association with tumour type, show that it is not only the extent of the surgical resection but the natural morbidity of the tumour type and other variables, such as peri-operative and intra-operative factors, that influence the outcome.

Albright *et al.,* (1996) in reviewing the extent of surgical resection in children with medulloblastoma tumours on outcome, conclude that the extent of residual tumour rather than the extent of surgical resection correlates with the prognosis in certain children. They found that children older than three years have a better outcome with total tumour resections compared with those who have not had a total resection.

An important methodological consideration is whether the extent of the surgical resection is defined by neurosurgical or neuroimaging criteria since the two estimates may differ. There could be little agreement between the neurosurgeon's report and the CT scan findings for a number of reasons, such as the timing of the reports, as there is often a delay between the operating procedure and the CT scan. Therefore, if possible, both estimates should be used (Packer, Sutton, D'Angio, 1986 in Ris & Noll, 1994). In the articles reviewed on the extent of the surgical resection and neuropsychological outcome, only Packer *et al.,* (1987) have taken this into account.

4.3. EXTENT OF SURGICAL RESECTION AND NEURO-PSYCHOLOGICAL FUNCTION

Although an inverse relationship between percent of tumour resected and mortality has been shown the relationship between percent of tumour resected and neuropsychological morbidity is inconsistent (Ris & Noll, 1994).

Surgery itself is not associated with acute effects on neuropsychological functioning according to Bordeaux *et al.,* (1988). They designed a study to provide both an understanding of the acute treatment effects and provide a baseline against which delayed sequelae could be evaluated. In this, they compared children treated by means of surgery only with those children treated by of surgery and radiotherapy. The groups were composed of children with tumours of heterogeneous diagnosis and locations, including posterior fossa location. The pre- therapy findings of both groups revealed that they performed within the average range on most neuropsychological measures. Deficits found at baseline were attributed to tumour-related effects and not to surgery. The pre- versus post-therapy test findings showed no significant changes for either group. The authors suggested that the results indicated that surgery and radiotherapy are not associated with acute effects on neuropsychological functions. Unfortunately the small sample size (14) influenced the statistical power to test for differences.

Three studies report that the extent of surgical resection of posterior fossa tumours had little impact on neuropsychological functioning. (Ellenberg *et al.,* 1987; Johnson *et al.,* 1994; Yang *et al.,* 1997)

Ellenberg *et al.,* (1987), in a prospective study, found that children who had gross total surgical (n=16) resections were more likely to have had fourth ventricle tumours. The partial surgical resection (n=24) group

comprised an equal number of fourth and third ventricle tumours, the remainder being hemispheric tumours. No significant difference between the mean IQ scores was found at the first, fourth or long-term post-operative follow-up assessments of the tumour groups. The amount of surgical tumour resection did not therefore impact on cognitive functioning. An attempt was made to control for the type of tumour by serial testing and having each child act as their own control.

Johnson *et al.,* (1994), in a retrospective study show that there was no significant difference between the extent of surgical resection (seven children had total resection: six children had partial resection) and IQ test scores or achievement test results in children treated for medulloblastoma brain tumours. However visual motor tracking and speed correlated with surgery and was significantly poorer for children who had partial surgical resections. The authors felt that this impaired specific skill may be confounded by other post-operative variables such as vasospasm, duration of surgery and intra -operative complications. Although all the children had craniospinal radiation of variable doses, two or three children were treated with chemotherapy protocols which included Methotrexate. Radiation dosage and chemotherapy treatment protocols are thus also potential sources of bias. The small number of full-study participants (13) is an added limiting factor. The authors verified the presence of the tumour and the extent of metastasis according to the staging system employed by Chang, Housepian and Herbert Jr (1969).

A retrospective study by Yang *et al.,* (1997) of 19 children with medulloblastoma brain tumours find that there was no significant difference in FSIQ scores between the group of children who had gross surgical resections and those who had partial surgical resections. Small patient numbers, unevenly distributed in the variable categories are a potential source of bias in this study in addition to the incomplete records documenting the extent of the surgical resection.

Conversely Packer *et al.,* (1987) in a retrospective study demonstrates that the extent of the surgical resection is significantly related to FSIQ, and this is the only study in the review which documents how the extent of surgical resection was verified. The extent of the surgical resection was according to the opinion of the surgeon at the completion of surgery and the post- operative CT scan (subtotal, near total, total) Post-operatively, all patients underwent a repeat CT scan, with and without intravenous contrast to determine the extent of the residual tumour and the size of the ventricles. An M stage as developed by Allen, Bloom, Ertel *et al.,* (1985) and Chang *et al.,* (1969), was used to verify the stage of the tumour and the stage of metastasis. Children with a total resection had a mean FSIQ of 98 compared with a mean FSIQ of 60 in children with a less than total resection. The number of the children in each surgical resection group is not specified but the morbidity of the sample is shown by the decreasing number of participants. The total number of medulloblastoma children who completed the testing is 17, which is a small sample, when compared to the original 43 children. The review is a retrospective study which the authors consider a flaw. However, they contend that multi-factorial issues such as pre and post-operative mental state as well as size of tumour exert an influence on outcome, although the association is not clear. Larger tumours which cannot be resected may cause permanent CNS damage prior to diagnosis.

4.4 ADJUVANT TREATMENT

Cranial radiation and chemotherapy are adjuncts to surgery for the treatment of children with posterior fossa brain tumours. These forms of adjuvant therapy carry a risk of neuropsychological and quality of life morbidity, the extent of which has only now been exposed as children are assessed over longer periods of time due to their improved life expectancy. The type of treatment regime advocated for posterior fossa tumours is dependent on the histological diagnosis of the tumour, the stage of the growth and the extent of the surgical resection.

Treatment strategies are in a continual state of flux as oncologists attempt to minimize the late radiation effects on the young developing brain. Some centres reduce the total radiation dose and fraction size in young children compared with older children and adults (Bloom & Glees, 1989). However, despite modification in the total dose and fractionation, there is increasing concern about intellectual impairment and poor quality of life in long-term survivors (Bloom & Glees, 1989; Duffner, Cohen, Thomas *et al.,* 1985; Duffner & Cohen, 1991; Ellenberg *et al.,* 1987; Kun *et al.,* 1983; Mulhern & Kun, 1985; Plowman 1999). In reviewing the literature on neuropsychological and quality of life effects of treatment, the researcher is faced with the fact of there having been changes in treatment regimes over time, as different centres adopt different strategies, which are not always considered and are thus a potential source of bias.

The most serious of the late effects of radiotherapy is necrosis resulting from high doses of radiation. This is considered an irreversible vascular condition which generally does not become manifest until approximately nine to twelve months following cranial irradiation and sometimes even years later (Crossen *et al.,* 1994). Radiation necrosis is a structural term, findings of which are based on either imaging or tissue pathology, or both methods. The definition implies toxic effects of dosage applied over time to some finite portion of normal brain (Crossen *et al.,* 1994). However a functional compromise of the patient's neuropsychological status can result without overt necrosis occurring and is defined as radiation encephalopathy and may resemble normal pressure hydrocephalus or leukodystrophy (Frytak in Crossen *et al.,* 1994).

The pathologic end state of radiation necrosis involves coagulation necrosis and gross demyelination of white matter in affected areas. The major observation from the long-term follow-up of radiation therapy is atrophy of tissues and organs (Crossen *et al.,* 1994).

According to Waldrop, Davis, Padgett *et al.,* (1998) proton MR spectroscopy provides biochemical information that can potentially affect treatment planning or prompt early intervention to prevent cognitive impairment. They found that in children with brain tumours, MR spectroscopy of brain tissue remote from the tumour reveals treatment related biochemical changes. Chemotherapy as a component of multitreatment protocol was associated with significant reduction in the biochemical ratios (NAA/Cr). A trend was shown for patients treated with chemotherapy before radiation therapy to have lower biochemical ratios suggesting that chemotherapy may alter subsequent effects of radiation therapy. In addition a trend was found for children treated with whole brain radiation to have lower biochemical ratios relative to those treated only with focal tumour therapy and to those not treated with radiation therapy.

4.5. SEQUENTIAL STAGES OF RADIATION REACTION AND NEUROPSYCHOLOGICAL FUNCTIONS

Sheline (1977) in Crossen *et al.,* (1994) describes sequential stages of radiation reaction and tissue injury for different types of brain tumours: acute reaction, early and late delayed reactions.

These range from many months to several years with the peak of symptoms emerging approximately 6 to 24 months after cranial irradiation.

A prospective study (Bordeaux *et al.,* 1988) on the acute effects (within one year of post-radiation treatment) shows that the treatment modalities of surgery only and surgery and radiotherapy are not associated with acute effects on neuropsychological functions. The pre- versus post-therapy neuropsychological test findings indicated no significant interval change for either group. The deficits in fine motor, psychomotor and timed language skills found at baseline testing were attributed to tumour-related effects. The absence of an interval change in the groups shows the importance of a follow-up time period of more than a year. At this stage

the deficits are more likely to emerge. In addition baseline pre-radiotherapy test scores are a valuable method of assessing change in neuropsychological test scores.

4.6. PROGRESSIVE INTELLECTUAL DETERIORATION

As early as the 1970's, it was suggested that mental handicap might be progressive or that patients might remain on a plateau of mental development following treatment for brain tumours (Glauser & Packer, 1991).

Subsequent research supports this claim of progressive intellectual deterioration in survivors of posterior fossa brain tumours treated by means of adjuvant therapy (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar, *et al.,* 1994; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Nishiyama *et al.,* 1994; Packer *et al.,* 1989).

Hoppe-Hirsch *et al.,* (1990) retrospectively assessed an original sample of 120 medulloblastoma subjects which revealed that the decrease in mortality reduced the number of subjects to a sample of 55 patients who were assessed five years post treatment. Five years post adjuvant treatment (12 patients having received intrathecal Methotrexate in the first years of the study), 58% of the sample patients had a FSIQ above 80 and 10% had FSIQ < 60. At the ten year post treatment, the sample was reduced to 13 patients who were tested. Of these 15% had an FSIQ >80, 35% had a FSIQ 60-80 and 46% FSIQ < 60. Unfortunately, as this is a retrospective study over a long period of time, subject attrition is a confounding issue in interpreting the results but nonetheless shows that FSIQ scores deteriorate over time.

Hoppe-Hirsch *et al.,* (1995) again show that, in survivors of medulloblastoma tumours (n=59) treated with adjuvant radiotherapy (chemotherapy did not include methotrexate) the FSIQ deteriorated

progressively. In the first year of the assessment, 43% of the sample had FSIQ of above 90, whereas at the 10 year assessment only 10% of the sample had a FSIQ above 90. The sample is compared with survivors of ependymoma tumours (n=37) who did not show the same FSIQ deterioration. In the first year of the assessment 63% of the ependymoma sample had a FSIQ above 90, while 56% of the sample maintained the FSIQ of above 90 at the 10 year assessment. School performance in the ependymoma group remained stable whereas in the medulloblastoma group school performance showed progressive deterioration over time, with 80% of the group in special education at the 10 year assessment.

Emotional and behavioural disorders were found in 20% of both groups of survivors. However, a progressive increase in the emotional and behavioural difficulties, such as emotional regression, inhibition, negative attitude, instability and attention difficulties, plagued 40% of the survivors at the five year assessment and 56% of the survivors at the ten year assessment. The authors state that the only difference between the groups is the radiotherapy treatment. The medulloblastoma survivors were treated with radiotherapy to the cerebral hemispheres whereas the ependymoma group were treated with radiotherapy to the posterior fossa.

In an editorial comment Richard D. Hayward (1995) suggests that the chemotherapy may also have been a contributing factor, as only 27% or 10 out of 37, of the ependymoma patients received chemotherapy compared with 76% or 45 out of 59 of the medulloblastoma patients.

Unfortunately, Hoppe-Hirsch, *et al.,* (1995) have not included the neuropsychological test battery or scores. A cut-off FSIQ score of 90 was used as it represented the border between normal and special school. It is therefore difficult to make adequate comment on the stated neuropsychological deficits of spatial orientation or verbal performance discrepancies.

A decline in FSIQ is shown by means of serial testing over a four year time span in a sample of 19 medulloblastoma children treated with whole brain radiotherapy; 14 of these also received adjuvant chemotherapy. (Radcliffe *et al.,* 1992) For the group as a whole the mean FSIQ fell from a baseline of 104 to 92 at follow-up. The decline in FSIQ occurred between the baseline testing and year two of follow-up, but none could be documented between years two and four. Children younger than seven years of Age-at-Diagnosis had a mean FSIQ loss of 27 points, compared with children over seven years of age who showed no significant decrease in FSIQ. Special education placements were needed for all the children treated at age less than seven years at Age-at-Diagnosis. Supplementary education was required for half the older children. All the children received a generally uniform amount of whole brain radiotherapy. The adjuvant chemotherapy comprises of cisplatinum, CCNU and vincristine. The authors hypothesize that the results are most likely due to the effects of the radiotherapy treatment but that the synergistic neurotoxic effect of the chemotherapy could not be ruled out on account of the small sample size. Although a deterioration in FSIQ was shown up to two years post-treatment, the same deterioration was not evident beyond the third and fourth years of treatment. The children in the study received intensive educational therapy which may in part account for the stabilization in intellect.

4.7 YEARS-SINCE-TREATMENT

Years-since-Treatment effects are complex when one considers specific neuropsychological functions (Dennis *et al.,* 1996) Nevertheless memory deficits have been found to increase with follow-up time (Packer *et al.,* 1989). Quality of life issues in survivors of medulloblastoma and ependymoma tumours have been reported as impaired psychosocial adjustment, the greater the Years-since-Treatment (Seaver *et al.,* 1994).

The studies of Ellenberg *et al.,* (1987); Hoppe- Hirsch *et al.,* (1990); Hoppe-Hirsch *et al.,* (1995); Moore, Ater and Copeland (1992); Nishiyama *et al.,* (1994); Packer *et al.,* (1989), suggest progressive deterioration in FSIQ in survivors of brain tumours with Years-since-Treatment. These studies are discussed in the following chapter.

4.8 INTERACTION OF AGE-AT-DIAGNOSIS AND YEARS-SINCE-TREATMENT

Dennis *et al.,* (1996) attempt to clarify the interaction of Age-at-Diagnosis and Years-since-Treatment, in predicting the outcome in a sample of 25 survivors of medulloblastoma brain tumours treated with surgery and radiotherapy. They found that Age-at-Diagnosis and Years-since-Treatment contribute separately to intellectual morbidity. PIQ varied with the chronological age of the child at tumour diagnosis (the younger children had lower PIQ's) and appeared to measure some general effects of cerebral insults, but was relatively constant in magnitude once established. VIQ declined with Years-since-Treatment and seemed to be less dependent on the stage of development at which the tumour was diagnosed. The ranges of Age-at-Diagnosis 0-12 years and Years-since-Treatment are 0 – 15 years respectively. In the younger Age-at-Diagnosis group < 4 years of age, the Years-since-Treatment is the longest (9 years compared with the other age cohorts of about 4 years) time span. The authors felt that failure to acquire knowledge might be a consequence of a time-limited brain pathology, interacting with environmental issues over time. The result was that the VIQ scores dropped with increasing Years-since-Treatment. In other words the medulloblastoma survivors failed to increase their verbal capacities at the same rate as other children of the same age, over the same period.

4.9. SURGERY AND RADIATION TREATMENT

Studies comparing children who do not undergo radiation as part of their treatment with those children whose tumours have been treated with radiation and surgery, show that regardless of the age at which the tumour was diagnosed, radiation treatment lowers IQ scores (Chadderton *et al.,* 1995; Chin & Maruyama, 1984; LeBaron *et al.,* 1988; Mulhern *et al.,* 1992; Roman & Sperduto, 1995).

Silverman, Plakes, Talent *et al.,* (1984) compared the late neuropsychological outcome of children treated for medulloblastoma tumours with craniospinal irradiation to their sibling controls. The patient's FSIQ score (average to low average range), compared with the non-irradiated sibling (average to bright average range) was found to be significantly lower but a striking difference was found between PIQ of patients compared with the sibling controls. All nine siblings scored at least 11 points higher on the PIQ than the irradiated patients. The effects on VIQ score were less dramatic but significant. Analysis of the FSIQ scores relative to whole brain radiation dose showed no significant effects. All patients had mild cerebellar dysfunction such as ataxic gait and dysdiadochokinesis and five patients had severe tremors. None of the neurological findings interfered with test performance and vision and hearing were normal in all but one patient. No correlation was found between FSIQ scores and objective physical or neurological findings.

The authors conclude that the decreased FSIQ scores of the patients are due to the treatment effects of radiation therapy. The use of sibling controls strengthens the conclusions of the hypothesis. The significant effects of the PIQ are discussed in terms of a decreased ability to assimilate new information and apply it to unfamiliar situations. This effect was more profound in the children younger than eight years of age at treatment who had not yet established strong reading skills or other rote functions mastered by the older patients. The patients' significantly lower

scores in arithmetic skills were discussed in terms of difficulty in ability to reason abstractly rather than a function which relies on over-learned skills. A trend towards increased effects of the treatment on cognitive function from Years-since-Treatment was also found. The authors conclude that serial evaluations are needed to explore this.

4.9.1 Radiation Dose Response Relationship

Children who undergo radiation treatment for brain tumours receive higher doses than those treated for leukemia and are therefore at greater risk for significant cognitive decline. Cousens, Waters, Said *et al.,* (1988) indicate that 1800 – 2400 centigray (Gy) of Whole Brain Radiotherapy Treatment (WBRT) is associated with an average decline of 10 FSIQ points, in children treated for leukemia. According to Ris and Noll (1994) and Roman and Sperduto, (1995), the data showing the relationship between radiation dose and outcome in children with brain tumours are inconsistent. The absence of a dose- response relationship may reflect a restriction in the range of the dose studied, as most children treated for posterior fossa brain tumours receive similar amounts of WBRT (Dennis *et al.,* 1996; Packer *et al.,* 1987; Sutton *et al.,* 1989). The articles by Mulhern (1994) and Ris and Noll (1994) of children treated with brain tumours find that there were few studies relating the radiation dose to decreased IQ scores. The effects of the range of radiation are better clarified in articles comparing the effects of radiation in children with posterior fossa tumours with those children treated for leukemia, as shown by Silber *et al.,* (1992). In a mixed group of ALL and medulloblastoma patients they found a greater FSIQ loss at two years post WBRT. In other words the higher the radiation dose the lower was the FSIQ. Thus a radiation dose of 36 Gy to the whole brain resulted in FSIQ scores of 8 points less on IQ testing than those children treated with 24 Gy, who achieved 12 points less on IQ testing than those treated with a radiation dose of 18 Gy. Young children showed a significantly greater negative effect of RT than older ones.

Recently Grill *et al.,* (1999) found long term intellectual fall outs in children with posterior fossa tumours according to the radiation doses and volumes. Long term cognitive impairment occurred in most of the patients as well as those receiving treatment only to the posterior fossa area. A significant correlation was shown between FSIQ scores and CSI dose. The higher the dose the lower the FSIQ score. The contribution of chemotherapy to the low scores according to the authors was not associated with impaired intellectual outcome. Half the subjects (10/21) did not receive chemotherapy. However no details are given as to how this finding occurred or the neuropsychologcal scores of those receiving chemotherapy compared to those not receiving chemotherapy treatment.

The outcome of restricted field radiation (RFRT) is also inconsistent as at present most treatments for children with brain tumours include RFRT. Dennis, Spiegler, Obsawin *et al.,* (1992) found deficits in working memory, but only in children with thalamic tumours treated with RFRT.

The differences in the fractionation, duration of RFRT and WBRT and whether treatment was completed or terminated due to complications, are often not reported in the results, making interpretation difficult.

4.9.2 Methotrexate Chemotherapy

Research on the effects of chemotherapeutic agents on cognitive functioning is minimal (Dowell *et al.*, 1989). An additional difficulty is that the chemotherapy protocols are not specified. Considerable evidence suggests that the use of methotrexate, intravenous or intrathecal, is associated with neuropsychological decline, particularly when used in conjunction with WBRT (Bleyer 1981; Duffner, Cohen, Anderson *et al.,* 1983; Duffner *et al.,* 1988).

As early as 1979, Hirsch and his French colleagues (Glauser & Packer, 1991) show that the treatment effects of surgery, radiotherapy and chemotherapy caused a decrease in IQ scores, although they had difficulty in deciding which treatment factors caused the decrease in IQ scores and behavioural difficulties found in the sample. Only 11% of the subjects who were treated for PNET had an FSIQ > 90, while 31% had an FSIQ <70. Craniospinal irradiation increased to doses of 5000 rads and chemotherapy included intrathecal methotrexate, vincristine and CCNU. Ninety three percent of the sample had emotional and behavioural disorders. Functional disability, assessed by Bloom's criteria, showed that 15% were in functional category 11 (mild disability, active life) and 12% in category 1V (total disability). Hirsch *et al.,* (1979) used a control astrocytoma group (surgery only treatment) to compare the deficits and found that 62% of the astrocytoma subjects had an IQ > 90. However, 59% of them had emotional and behavioural problems, suggesting that factors, other than treatment of radiotherapy, chemotherapy and surgery, were associated with the difficulties.

Studies of children with ALL have suggested that children treated with a combination of CNS radiation and chemotherapy, intrathecal methotrexate, may have learning disabilities, perceptual difficulties and in some cases dementia (Meadows & Evans; 1976). According to Duffner *et al.,* (1983) and Waber, Tarbell, Kahn *et al.,* (1992) it is likely that prophylactic radiation of the CNS in children, together with intrathecal methorexate, may lead to a mild but significant lowering of IQ. Conflicting results regarding CNS prophylactic therapy on cognition appear to be due to inconsistencies in methodology (Fletcher & Copeland, 1988). More recently, Butler, Hill, Steinhertz *et al.,* (1994) find that cranial radiation in conjunction with methotrexate is associated with impairment in nonverbal intelligence, perceptual abilities and a susceptibility to distraction.

4.9.3 Nonmethotrexate Chemotherapy

The role of chemotherapy in posterior fossa tumours depends on the histological diagnosis. The Grade 1 and Grade 11 cerebellar astrocytomas are resistant to chemotherapy (Karabus, 1996). The platinum compounds and several single agents are however the most effective treatment for ependymoma brain tumours (Karabus, 1996), while only short duration responses to single or multiple agent chemotherapy regimes are reported for brain stem glioma treatment (Levin, 1985). Medulloblastoma / primitive neuroectodermal tumours appear to be the most chemosensitive. Alkylators such as cyclophosphamide and melphalan and the platinum compounds are single active agents. Combinations such as 8-drugs-in-one-day devised by Bleyer and her colleagues, MOPP or CCNU, vincristine and procarbazine have shown some positive effect (Karabus, 1996). The few randomized trials performed suggest a marginal benefit for the addition of chemotherapy only in patients at high risk, which is described as young age, incomplete resection or advanced Chang stage (Evans *et al.,* 1990; Pezotta, Montezemolo, Arrigoni *et al.,* 1996;Tait, Horton-Jones, Bloom *et al.,* 1990).

The blood brain barrier (BBB) and the blood cerebrospinal fluid (CSF) barrier have decreased permeability in patients with CNS malignant tumours and are therefore major obstacles to anti-tumour drug delivery. When visualized on contrast-enhanced imaging, the surrounding tumour infiltrated brain has a relatively intact barrier. Even if the main bulk of the tumour has a permeable vascular endothelium, the edge of the tumour, in which tumour proliferation is most rapid, has decreased permeability to anti-tumour agents (Williams, Henner, Roman-Goldstein *et al.,* 1995).

4.9.4 Complications Of Chemotherapy

4.9.4.1 Platinum- Based Chemotherapy Hearing Loss

Institutions use different chemotherapy protocols over varied periods of time, with the result that the effects of the chemotherapeutic agents on the neuropsychological functions of children with posterior fossa brain tumours are difficult to extrapolate. The interactive, synergistic effects of methotrexate chemotherapy and radiotherapy are well documented. The interaction may also apply to modern platinum based chemotherapy. Thus cisplatin is cumulatively toxic to the inner ear, leading first to high tone hearing loss, and this is synergised by prior radiotherapy encompassing that organ (Plowman, 1996). The hearing loss caused by cisplatin is, however irreversible (Duffner *et al.,* 1988), while hearing loss extending to speech can limit cognitive development (Mulhern, 1994).

Marked intellectual deficits have been observed following platinum/brain radiation scheduling (Duffner *et al.,* 1988; Vijayraghaven, Brock, Monson *et al.,* 1993).

Differences in toxic profiles between carboplatin (primarily myelosuppression) and cisplatin (mainly nephrotoxicity, peripheral neuropathy and ototoxicity) have led to their combination in regimes for a variety of malignancies (Freilich, Kraus, Budnick *et al.,* 1996). Castello, Schiavetti, Padula *et al.,* (1995) found no evidence of ototoxicity in a group of low grade astrocytoma children treated with chemotherapy protocols which included carboplatin. Freilich *et al.,* (1996) found that hearing deteriorated in five out of 14 children under six years of age, diagnosed with malignant brain tumours and treated with surgery and combinations of cisplatin and vincristine, cyclophosphamide and Etoposide followed by consolidation with carboplatin, ThioTEPA. Etoposide and autologous bone marrow rescue. The authors conclude

that ototoxicity is related to the consolidation therapy and is probably due to the high dose of carboplatin used prior to cisplatin therapy, aminoglycosides and cranial irradiation in one patient. According to Williams *et al.,* (1995) despite these side effects carboplatin and Etoposide with BBB disruption are sometimes an active treatment in malignant astrocytomas and have produced dramatic responses in PNET.

4.9.4.2 Vincristine

Vincristine, one of the biologically active alkaloids, is used in the treatment of solid tumours, lymphoma and lymphoblastic leukaemia (Roux, 1987). Neurotoxicity is dose limiting in vincristine therapy while RT may enhance vincristine neurotoxicity (Byfield, 1972 in Roux, 1987).

Vincristine causes peripheral neuropathy which improves after treatment stops. However, without due care muscular contractures may occur (Ryan and Emani, 1983). Neuromyopathy is present in all patients treated with vincristine for more than two months. Vincristine does not appear to cross the BBB, but intrathecal administration of vincristine has been uniformly fatal. The drug is rapidly distributed and bound to neurons, causing neuronal death (Gaidys, Dickerman Walters *et al.,* 1983) Neurotoxicity due to vincristine, occurs outside the CNS, in the absence of intrathecal administration (Roux, 1987).

The outcome of radiation and an adjuvant chemotherapeutic regimen of vincristine, cisplatin, and CCNU is discussed with regard to the toxicity of the adjuvant chemotherapy in a study of 63 children with posterior fossa medulloblastoma tumours (Packer *et al.,* 1994). Forty seven percent of patients developed significant audiological toxicity, usually after the fourth dose of cisplatin. but only one child required a hearing aid at the end of treatment and another developed a progressive hearing loss three years following completion of treatment and now requires a hearing aid. Renal toxicity developed in 13 children, but no child developed clinically

significant kidney dysfunction. Eleven children required platelet transfusion. Severe vincristine-related peripheral neuropathy was relatively infrequent. Seizures or other neurotoxicity due to the chemotherapy were not found. The authors state that using a modified dose of cisplatin is a means of allaying the concerns over the ototoxicity of the drug. However, a head-to-head trial of any other drug regime compared with CCNU, cisplatin and vincristine regimen has never been undertaken and there are no data to determine the potential toxicity of other adjuvant drug regimens.

4.10. SUMMARY

- Tumour type and the associated morbidity of the brain tumour are interrelated factors when investigating the effects of the surgical resection on outcome. How the resection is defined is a methodological consideration in the evaluation of outcome.

- Surgical resection per se is not usually associated with cognitive morbidity and quality of life outcome is generally not considered.

- There is no clear evidence that the extent of the surgical resection is associated with intellectual decline.

- An overall difficulty in the evaluation of surgical resection is the heterogeneity of the surgical procedures as well as the intraoperative support and peri-and post-operative management which are sources of variance which should be taken into account when evaluating the overall treatment outcome.

- Cranial radiation and chemotherapy are often adjuncts to surgery for the treatment of posterior fossa tumours. These are in a continual state of flux in an attempt to improve the neuropsychological functioning and quality of life outcomes on the developing brain. A

detailed discussion of factors pertaining to neuropsychological and quality of life outcome, based on the literature review found in Appendix H, is presented in Chapter 6.

- The sequential stages of radiation reaction for different types of brain tumours may range from six to 24 months. In the acute stage, within one year post-radiation treatment impaired neuropsychological scores may not be found in posterior fossa brain tumour survivors (Bordeaux *et al.,* 1988). However, progressive intellectual deterioration is reported by some researchers (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Nishiyama *et al.,* 1994; Packer *et al.,* 1989) or patients may remain at a plateau of mental development (Bamford *et al.,* 1976).

- A correlation between radiation dose and volume and cognitive decline in scores is described, but the contribution of chemotherapy to the low scores is not clearly illustrated.

- Years-since-Treatment effects are complex and are discussed in greater detail in later chapters as well the interaction of Age-at-Diagnosis and Years-since-Treatment.

- The contributions of chemotherapy to the neuropsychological outcome are difficult to extrapolate and are presumed to be interactive unless a longitudinal design is employed to partial out the effects of each type of treatment.

- Hearing loss is a complication following cisplatin chemotherapy. Vincristine causes neuropathy which improves after treatment stops but RT may enhance vincristine neurotoxicity.

CHAPTER 5

SELECTED POST-TREATMENT COMPLICATIONS

5.1. TRANSIENT CEREBELLAR MUTISM

In 1985, two separate studies Rekate, Grubb, Aram *et al.,* (1985) and Yonemasu, (1985), in Humphreys (1989), define transient cerebellar mutism, as the temporary absence of speech and sound in an awake and conscious patient. This was first recognised as a complication following surgery for the resection of posterior fossa tumours in children. Although Hirsch *et al.,* (1979) acknowledge the problem of speech disorders including post-operative mutism in their patients treated for medulloblastoma tumours, they do not expand on the entity of mutism which can occur as a post-operative phenomenon in some children who have recently had surgery for cerebellar-tumours (Humphreys, 1989)

5.1.1 Definition of the Syndrome

Humphreys *et al.,* (1989) cite that the syndrome first described by Yonemasu and Rekate *et al.,* developed after the removal of very large fourth ventricular tumours. Post-operative speech loss occurred after a brief interval of normal speech. The mute state persisted for one to three months and was followed by a severe cerebellar speech disturbance with a subsequent return to normal patterns of speech. Despite the presence of severe cerebellar ataxia, the children were otherwise alert and exhibited no obvious brain-stem signs. The children showed no disturbance of phonation, were able to comprehend words well and to communicate with others by gesture. Yonemasu attributed the phenomenon to aphasia rather than mutism and cited an earlier paper by Sakai (1980) on the subject. Rekate *et al.,* (1985) on the other hand

favoured a cerebellar rather than a brain-stem process. The absence of long tract and other cranial nerve dysfunctions supported their hypothesis.

Debate on the aetiology is rife and, since the syndrome was first described, many other cases have been reported (Wisoff and Epstein, 1984; Humphreys, 1989; Ferrante *et al.,* 1990; Asamoto, Ito, Suzuki *et al.,*, 1994; Cochrane *et al.,* 1994; Crutchfield, Sawaya, Meyers *et al.,* 1994; Kingma, Mooij, Metzemaekers *et al.,* 1994; Van Dongen, Catsman-Berrevoets and Van Mourik 1994; Dailey, McKhann II and Berger, 1995; Pollack *et al.,* 1995; Van Calenbergh, Van der Laar, Plets *et al.,* 1995; Ersahin, Mutluer, Cagli, *et al.,* 1996; Jones, Kirollos and Van Hille 1996; Liu, Phillips, Molloy *et al.,* 1998)

The syndrome, although uncommon, is now a well-documented complication. The incidence of transient cerebellar mutism in children with posterior fossa tumours is reported as 8.2% by Dailey *et al.,* (1995), 5.7% by Cochrane *et al.,* (1994) and 8.5% by Pollack *et al.,* (1995). Risk factors appear to be large tumour size, midline location, brain stem and fourth ventricle involvement, hydrocephalus and post-surgical oedema or meningitis (Van Calenbergh, *et al.,* 1995).

The types of posterior fossa tumours associated with mutism are; medulloblastoma, astrocytoma and ependymoma (Ersahin *et al.,* 1996; Ferrante *et al.,* 1990; Pollack *et al.,* 1995). However 61% of the cases occurred after the removal of a medulloblastoma brain tumour. (Van Calenbergh *et al.,* 1995)

The literature suggests that 90% of the children with cerebellar mutism are less than 10 years old (Van Dongen *et al.,* 1994), that the mean age of the children is 7.5 years at onset of the mutism syndrome and that 72% of the cases occur in boys. All cases are transient and the average interval of mutism is 6.5 weeks (Van Calenbergh *et al.,* 1995).

5.1.2 Visual Impairment Associated With Mutism

Visual impairment associated with mutism after posterior fossa surgery has recently been described in four children (Liu *et al.,* 1998) The authors report that they are not sure if they are describing a new phenomenon or one unrecognized in some of the previously reported children. Pre-operatively, none of the children had visual complaints apart from diplopia. Post-operatively all four children became mute and withdrawn. Neuro-opthalmology consultation revealed that no child blinked to threat or followed, although the pupils were reactive to light. Each child had papilloedema: one child reached for an object of interest while another had an inconsistent optokinetic response. Visual impairment improved roughly in parallel with the recovery of speech. Within three weeks to six months the disc swelling had resolved and the optic discs retained their normal colour. Follow-up neuroimaging did not reveal any causative lesion in the visual pathways. The authors discounted a variety of causes for the visual loss such as retinal or choroidal ischaemia, errant shunts and cortical blindness. They hypothesize that the children suffered from visual inattention caused by damage to the cerebellar structures having an influence on higher cortical functions including attention and language. They suggest that the cerebellum may be important in tasks that require rapid shifts of attention between auditory and visual stimuli as suggested by Courchesne, Townsend, Akshoomoff *et al.,* (1994)

5.2 ENDOCRINE DYSFUNCTION

5.2.1 Growth Hormone Deficiency (GHD)

According to Duffner and Cohen (1991) a review of retrospective studies, suggests that cranial irradiation will cause GHD in up to 80% of children with brain tumours and that the biochemical effects can be identified as early as three months following completion of radiation.

Several retrospective studies demonstrate that GHD is the first and most frequent pituitary deficiency to occur in children who receive cranial irradiation for tumours distant from the hypothalamus and pituitary region (Brauner, Rappaport, Prevot *et al.,* 1989; Duffner *et al.,* 1985; Johnson *et al.,* 1994) A prospective study comparing a group of patients who received cranial irradiation only with a group who received craniospinal radiation show that pituitary GH secretion is more rapidly impaired in children than adults (Lam, Tse, Wang *et al.,* 1987 in Brauner *et al.,* 1989). However, the effect of GH impairment was minimal two years after radiation and most of the growth retardation found in children treated with craniospinal radiation was due to the additional spinal radiation. The children with medulloblastoma and ependymona brain tumours who received an irradiation dose between 31-42 Gy, lost almost 1.5 standard deviations of height after two years craniospinal radiation.

GHD does not appear to be reversible, as the children in the Duffner (1985) study remained GHD for as long as eight years following treatment. Most GHD children with brain tumours will grow on GH treatment. Lannering *et al.,* (1990) found that 57% of the sample of adults treated for brain tumours as children had short stature. Although the GH had been given to all prepubertal patients with GHD, it had been started too late to prevent short stature.

Meanwhile there is a concern that administration of GH may induce recurrent tumours (Ogilvy-Stuart, Ryder, Gattameni *et al.,* 1992). A reassuring study on 1262 children with brain tumours treated with GH shows that children with the more common types of brain tumours, such as glioma and medulloblastoma, do not seem to be at excessive risk of recurrence (Moshang Jr, Rundle, Graves, *et al.,* 1996).

An additional cause of short stature in children treated for brain tumours, is failure of the vertebral body growth due to radiation (Chin and Maruyama, 1984). The adverse influence of young age at Time-of-

Treatment is reported by Duffner and Cohen (1991) who find that the younger the child at the time of spinal radiation, the worse the subsequent disproportion. A loss of 9cm in height is anticipated in children treated with spinal radiation at the age of one year compared to a 5.5cm loss in children radiated at ten years of age. As GH treatment will not improve spinal growth, height will be significantly affected.

Adjuvant chemotherapy also adversely affects height (Duffner and Cohen, 1991; Mulhern *et al.,* 1989). Poor nutrition and the associated side effects of chemotherapy of nausea, vomiting and lack of appetite are likely to increase the role of poor nutrition in growth failure (Duffner and Cohen, 1991).

Endocrine deficiencies and growth retardation in height at less than the fifth percentile appear in a retrospective study where of 9 out of 14 children with brain tumours have been treated with radiation (Moore, Copeland, Reid *et al.,* 1992). A study of a twin who was treated for a medulloblastoma, indicates that her height was 3.6cm shorter than that of her twin one year after treatment. Three and a half years later, the difference in height had increased to 7cm but has not changed since then. An interesting aspect of the study is that the treated twin was not short in stature compared with Japanese girls of the same age (Nishiyama *et al.*, 1994).

Growth hormone supplementation has not been found to affect cognitive function. Dennis *et al.*, (1992), for example found no difference in memory scores between children and adolescents who are being treated for brain tumours and receiving growth hormone supplementation and those not supplemented. However, the authors did show that certain combinations of age and hormone variables produce deficient serial order memory scores but state that further research is needed.

Weight measurement is not often reported and this may be due to the fact that few abnormalities in weight are reported. Li, Winston and Gimbrere (1984), reveal that in 96 survivors of brain tumours treated with surgery and adjuvant therapy, only 2% had a weight of below the 3rd percentile and 13% were above the 97th percentile. A Japanese study (Onoyama, Mitsuyuki, Takahashi *et al.,* 1975) shows that stunted growth of more than 2 standard deviations below the mean was found in 36% of the brain tumour survivors treated with surgery and radiotherapy. However, only eight children, or 19% of the sample, had an abnormal decrease in weight of more than two standard deviations. Bamford, Jones Peason *et al.,* (1976) also report a low incidence, 23%, of weight below the 25th percentile, in a sample of long term survivors of brain tumours.

Robertson, Ackerman and Traynelis (1997) surprisingly report increased height in patients with medulloblastoma tumours. The pre-operative height and weight were documented and compared with a control group of cerebellar astrocytoma tumour patients. A significant number of patients presenting with medulloblastoma brain tumours had attained increased height but maintained normal weight, which was inconsistent with the weight loss generally observed with neoplasms. A similar finding in height was not observed in the astrocytoma brain tumour group who were of average height and low average body weight. The authors conclude that medulloblastoma brain tumours may be influenced by GH production or may produce growth factors in vivo.

5.3. SEIZURES

Virtually any insult to the developing nervous system can result in seizures. The terms seizures, convulsions and epilepsy are sometimes used synonymously but do not in fact refer to the same phenomenon although they have the same common denominator – involvement of

abnormal electrical activity or discharge of cerebral neurons (Spreen *et al.,* 1995).

The cerebellum therefore does not have the ability to generate seizures. As suggested by Cohen and Duffner (1984) seizures as a presenting symptom of posterior fossa tumours are rarely reported, as this implies spread of the tumour into other areas, unlike hemispheric tumours in which seizures as a presenting symptom occur in 30% to 60% of cases. In cortical tumours in childhood, seizures are second only to headache as the most common presenting symptom (Giles, Sobel, Leviton *et al.,* 1992; Penfield, Erickson and Tarlov *et al.,* 1940; Piepmeier, 1987). Meanwhile Packer, Sutton, Patel *et al.,* (1994) report the incidence of seizure control following tumour surgery for childhood low grade gliomas. Tumour-related seizures are more frequently associated with slow growing, infiltrating neoplasm and they may have their origin in the tumour-free cortex adjacent to the neoplastic nidus.

As epilepsy is a symptom of disease rather than a disease itself, the investigation of post-operative seizures depends on knowledge of potential causes. These may be due to shunt complications, spread of the tumour into the cerebral cortex, electrolyte imbalance or cranial irradiation.

An 11.5% seizure disorder was reported following treatment in a sample of brain tumour children, a higher incidence occurring in those children with supratentorial tumours (Gjerris, 1976). A similar incidence of post-operative seizures is found by Hoppe-Hirsch *et al.,* (1990), five years after treatment, in a sample of 84 medulloblastoma brain tumour patients. At the ten year post-treatment assessment, the number of survivors reported with epilepsy was the same as at the five year assessment (nine patients) but due to the decrease in the size of the sample, the incidence was reported as 26%.

A long-term retrospective study of children treated with irradiation for brain tumours indicates that epilepsy emerged as the only significant variable independently associated with poor cognitive function (Syndikus *et al.*, 1994). Moreover, Ellenberg *et al.,* (1987) report that two children with hemispheric tumours and a history of seizures prior to cranial irradiation had the lowest FSIQ scores in the sample.

It is well documented that seizures and anticonvulsant medication may contribute to neurobehavioural morbidity (Kun *et al.,* 1983; Syndikus *et al.*, 1994).

According to Spreen *et al.,* (1995), the developing brain is more susceptible to repeated seizure activity, with resulting cell death or at least inhibition of continuing cell enlargement and the formation of more complex connections between neurons, so that the effect on intelligence in children is more profound. Mental retardation following seizures was found to be more common in children if the seizures have been uncontrolled for two years and if there was an early onset (Huttenlocher and Hapke, 1990).

In a detailed study of neuropsychological performance, O'Leary, Lovell, Sackellares *et al.,* (1983) reveal that early onset, regardless of seizure type, places a child at risk of cognitive dysfunction. However it is not possible to examine the consequences of a convulsant disorder independently of the underlying aetiological condition. Accordingly epilepsy - recurrent and frequent seizure activity – is often associated with motor disorders (Spreen *et al.,* 1995).

5.4 SUMMARY

- The incidence of transient cerebellar mutism in children with posterior fossa tumours varies from 8.5% to 5.7%. Visual impairment associated with mutism has recently been described and improvement

parallels recovery of speech associated with improvement in the mutism condition.

- Growth hormone deficiency due to cranial irradiation occurs in up to 80% of children with brain tumours and is not reversible. An adverse influence of young Age-at-Diagnosis at Time-of-Treatment causes short stature in which there is failure of the vertebral body to grow due to retardation. Adjuvant chemotherapy adversely affects height, such that height may be below the 5th percentile.

- Weight is often not reported as few abnormalities have been shown.

- Recurring seizures, as presenting symptoms in posterior fossa tumours are rarely reported as the cerebellum does not have the ability to generate seizures. However seizures as a presenting symptom may be associated with slow-growing tumours which have their origin in the tumour-free cortex adjacent to the neoplastic nidus (Packer *et al.*, 1994).

- An 11% post-operative incidence of seizure disorder in medulloblastoma survivors is reported.

- Epilepsy is associated with poor cognitive functioning in brain tumour survivors treated with cranial irradiation.

- The developing brain is more susceptible to repeated seizure activity and the early onset of a seizure disorder places a child at risk for cognitive dysfunction.

CHAPTER 6

LITERATURE REVIEW OF NEUROPSYCHOLOGICAL FINDINGS AND QUALITY OF LIFE ISSUES

6.1. INTRODUCTION

In an extensive literature review on paediatric brain tumours there is no distinct neuropsychological profile for paediatric brain tumours (Glauser and Packer, 1991;Ris and Noll, 1994). This is not unexpected given the broad spectrum of tumours studied and the concomitant wide array of treatments given to both children and adult survivors over differing time spans.

A deficit pattern of attention, memory and nonverbal skills with the relative preservation of language ability is found in patient populations such as those with congenital hydrocephalus or head injury, who sustain damage to the cerebral white matter. Fletcher and Copeland (1988) reported the same deficit pattern in children treated with CNS prophylaxis diagnosed with ALL and treated with cranial radiation.

Moore, Ater *et al.,* (1992) discussed this pattern in children diagnosed with brain tumours in infancy and treated with cranial irradiation, whose weakest scores were in PIQ and visual spatial ability. The authors postulated that tasks emphasizing nonverbal processing skills (believed to be subserved by the non-dominant hemisphere) are more vulnerable to white matter damage caused by radiation than those subserved by the dominant hemisphere. This hypothesis is based on findings that in normal right-handed adults, the blood flow is greater in the cerebral white matter of the right than of the left hemisphere (Gur *et al.,* 1980 in Moore, Ater *et al.,* 1992). Greater white matter volume is then presumed in the right

rather than the left hemisphere. The vulnerability of white matter to radiation induced damage should therefore be manifested to a greater degree in the hemisphere with the greatest proportion of white matter. Deficits would then be more nonverbal than verbal in nature. The pattern of relative preservation of language skills supports the hypothesis that dominant hemisphere functions are less vulnerable to the effects of cranial irradiation (Fletcher and Levin in Moore, Ater *et al.,* 1992).

Further evidence to support the loss of white matter was found by Mulhern, Reddick Palmer *et al.,* (1999). They showed that patients treated for medulloblastoma brain tumours by means of surgery, radiation and chemotherapy had significantly less normal white matter and significantly lower FSIQ scores than patients treated by means of surgery for astrocytoma brain tumours. The authors concluded that irradiation or chemotherapy treatment induced destruction of normal white matter. This can partially explain intellectual and academic achievement deficits among medulloblastoma survivors. Their obtained model suggests that variations in the subjects normal white matter may provide a more direct explanation for variations in FSIQ scores than the patient's age at treatment.

The literature review covers a time span of twenty five years, 1975 to 2000. Appendix H lists the papers found through a computer search and review of principle professional journals in the areas of paediatric oncology. Papers presented in the review include both the acute (less than one year post treatment) and chronic effects of treatment on neuropsychological and quality of life outcome measures. Although the review by Ris and Noll (1994) selected one year after treatment as a point of demarcation, other reviews (Crossen *et al.,* 1994; Glauser & Packer, 1991; Roman & Sperduto, 1995) have included subjects in both the acute and chronic treatment stages. The review by Mulhern (1994) concentrates on late effects, which occur after completion of medical treatment, at about two or more years from the time of diagnosis. The inclusion of

subjects in both early and late treatment stages in the present review should give one a better idea of the vulnerability of the functional status of the childhood survivors.

The review focuses on studies in which the outcome for children with posterior fossa brain tumours can be ascertained. It includes studies of childhood tumours that provide illustrative contexts or relevant contrasts to posterior fossa brain tumours and studies using only specific types of posterior fossa brain tumours such as medullblastoma, astrocytoma, ependymoma or brain stem glioma brain tumours. As there are few articles on the social, behavioural and health related quality of life of brain tumour survivors, selected studies on children surviving ALL have also been included. ALL and brain tumours are fatal if untreated, both disease states are carcinogenic and the treatment for both diseases involves radiotherapy and chemotherapy. The ALL studies should therefore add pertinent information about treatment related toxicity.

6.2 DETERMINANTS OF NEUROPSYCHOLOGICAL AND QUALITY OF LIFE OUTCOME AFTER POSTERIOR FOSSA BRAIN TUMOURS IN CHILDHOOD

Studies of cognitive morbidity have explored how neuropsychological and quality of life outcomes are related to several variables. These include factors in the child such as SES and Age-at-Diagnosis: features of the tumour (Chapter 2), factors associated with pretreatment (Chapter 3), treatment (Chapter 4) complications following treatment (Chapter 5), Time-since-Treatment and the interaction among these factors.

6.2.1 The influence of Socio-economic Status (SES)

SES is an index that reflects diverse factors: these include nutrition, quality of home environment, parental education, quality of school and

quality of medical care. Although most of the studies reviewed reported that they had considered SES in the sample no study found that SES had contributed to either a good or poor outcome. Ris and Noll (1994) stated that little research has considered these factors. Two studies (detailed below) conducted at Groote Schuur Hospital, in Cape Town, South Africa, support the crucial role of SES in understanding neurobehavioural outcome.

Roux (1987) compared survivors of ALL treated with RT and chemotherapy at Groote Schuur Hospital to children with solid tumours treated without RT and chemotherapy. The ALL children had significantly lower scores on growth, intellectual measures, neurological status and miscellaneous organ damage. Low scores were attributed to CNS injury caused by RT, with or without a synergistic effect of methotrexate. In this study the author suggested that psychosocial adaptation was surprisingly good, relative to poor family functioning found in a minority of the families in the sample. Evidence of educational disadvantage was obtained from the results of the IQ test scores on the Senior South African Individual Scale (SSAIS) of certain children. These children came from relatively deprived circumstances, but the test did not have norms for the disadvantaged children such as that of the Senior South African Individual Scale Revised (SSAIS-R) version. A global pattern of impairment with negative trends in verbal reasoning, abstract language, memory and the use of spatial concepts was shown.

In a prospective study of 1134 children with head injuries, Hemp (1989) found a high incidence of psychosocial adversity in all the head injured subjects as well as the control group with orthopaedic injuries. A high psychosocial adversity score contributed to predicting a bad rather than a good neuropsychological outcome.

6.2.2 Age-at-Diagnosis

The terms Age-at-Diagnosis and Age-at-Treatment are used interchangeably in the literature. The association between Age-at-Diagnosis and neuropsychological impairment has been difficult to specify because of the variations in the definition of "younger". Some investigators define young age to be three years old or less (Hoppe-Hirsch *et al.,* 1990; Johnson *et al.,* 1994; Nishiyama *et al.,* 1994; Sutton *et al.,* 1989); others as below six years (Chapman *et al.,* 1995; Chin & Maruyama, 1984; Ellenberg *et al.,* 1987; Jannoun & Bloom, 1990; Mulhern & Kun, 1985; Seaver *et al.,* 1994) yet others as below seven years (Ellenberg *et al.,* 1987; Packer *et al.,* 1987; Radcliffe *et al.,* 1992); or even as below eight years (Chin & Maruyama, 1984). Moore *et al.,* (1992) and Sutton *et al.,* (1989) find that at Age nine to ten years-at-Diagnosis neuropsychological functions were relatively unaffected.

A problem in the assessment of age at diagnosis is the inclusion of a sufficient number of children across a broad range of ages which will yield conclusive results. All six longitudinal studies reviewed (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Koa *et al.,* 1994; Mulhern *et al.,* 1989; Radcliffe *et al.,* 1992) encountered this difficulty.

6.2.3 Time-Since-Treatment

Time is an important moderator of outcome. With time cognitive status may improve, relapse, plateau, exacerbate old deficits or change the rate of development.

An interrelationship between Age-at-Diagnosis, Time-since-Treatment and lower FSIQ score with increasing Time-since-Treatment has been reported by several researchers (Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Nishiyama *et al.,* 1994; Sutton *et al.,* 1989).

Silber *et al.,* (1992) use a multiple regression model to predict the final FSIQ score based on the initial FSIQ score, dose of irradiation and age at time of irradiation. The application of this model predicts higher FSIQ score with lower dose and increasing age at radiation. The authors found that the following factors are not significant in predicting FSIQ: SES; gender; type of IQ measure used; diagnosis (ALL or PNET tumour); if tested prior to two years from treatment or after two years from treatment; presence or absence of surgery; post-operative infection; presence or absence of shunt and inclusion of methotrexate chemotherapy. These factors have been disputed by other researches and are discussed under the relevant heading in the present literature review.

The importance of time factors is well illustrated in the longitudinal studies (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Koa *et al.,* 1994; Mulhern *et al.,* 1989; Radcliffe *et al.,* 1992)

These studies show that the cognitive functioning of the children fluctuate and illustrate that young age at testing and diagnosis interact over time. The two studies which had very young children in the sample (Gajjar *et al.,* 1994; Mulhern *et al.,* 1989) illustrated that the timing and administration of chemotherapy either improved or decreased cognitive functioning. Duffner *et al.,* (1988) only found significant declines in cognitive functioning two years after administration of treatment by means of surgery, radiotherapy and /or chemotherapy whereas Radcliffe *et al.,* (1992) showed declines in cognitive functioning occurred from baseline to year two after treatment and thereafter cognitive functioning appeared to plateau in year four. Ellenberg *et al.,* (1987) found a similar trend in that cognitive functions declined from year one to year three and thereafter reached a plateau. Koa *et al.,* (1994) are the earliest researchers to demonstrated that perioperative factors contribute to the decline in cognitive functioning from baseline testing to year four.

Thus the importance of perioperative factors as an additional adverse influence on the decline of cognitive functioning needs to be taken into account in future studies. Although longitudinal studies measure the child's performance compared to normative data that change with age, they provide little information on the child's future or past course of development. This approach fails to model behaviour as a function of time. According to Fletcher and Taylor in Broman and Michel (1995) the process of development marked by age and reflecting change are the important factors.

However Dennis *et al.,* (1996) found that Age-at-Diagnosis and Time – since - Treatment made separate contributions to intellectual morbidity.

To summarise Age-at-Diagnosis, Time-since-Treatment, tumour type and treatment variables are complex factors in the assessment of change and prediction of outcome following treatment for posterior fossa brain tumours.

6.3 MEASUREMENT ISSUES IN OUTCOME STUDIES OF CHILDREN WITH POSTERIOR FOSSA BRAIN TUMOURS

6.3.1. Methodological Considerations

In clinical research, it is not possible to control all potential threats to internal validity and firmly established cause and effect relationships. Moreover, theoretical approaches to study design have led to the use of outcome measures that may fail to illuminate treatment effects. The following factors were considered in reviewing the literature:

6.3.2 Types of Designs

6.3.2.1 Retrospective Studies

Of the sixty three studies reviewed, forty four studies or 70% utilized retrospective designs:

(Bamford *et al.,* 1976; Bauld *et al.,* 1998; Broadbent *et al.,* 1981; Chadderton *et al.,* 1995; Chapman *et al.,* 1995; Chin & Maruyama, 1984; Cohen *et al.,* 1993; Danoff *et al.,* 1982; Dennis, Spiegler, Fitz *et al.,* 1991; Dennis, Spiegler, Hoffman *et al.,* 1991; Dennis *et al.,* 1992; Dennis *et al.,* 1996; Dennis *et al.,* 1998; Eiser *et al.,* 1981; Feeney *et al.,* 1992; Feeny *et al.,* 1993; Grill *et al.,* 1999; Hetherington *et al.,* 2000; Hirsch *et al.,* 1979; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Jannoun & Bloom *et al.,* 1990; Jenkin *et al.,* 1998; Johnson *et al.,* 1994; Jordan *et al.,* 1995; Kimmings *et al.,* 1995; Lannering *et al.,* 1990; Le Baron *et al.,* 1988; Li *et al.,* 1984; Moore *et al.,*1992; Moore *et al.,* 1994; Mostow *et al.,* 1991; Mulhern *et al.,* 1999; Nishiyama *et al.,* 1994; Noll *et al.,* 1999; Onoyama *et al.,* 1975; Packer *et al.,* 1987; Riva *et al.,* 1989; Roux, 1987; Seaver *et al.,* 1994; Silverman *et al.,* 1984; Syndikus *et al.,* 1994; Yang *et al.,* 1997)

Advantages of this type of design:

- They are cost effective, time efficient, utilize large samples from a given population, may be the only feasible approach to studying rare diseases such as paediatric brain tumours and provide meaningful information about the way the variables function in relation to one and other.

Disadvantages which may lead to bias:

- The problem of backward contingency, incomplete or inaccurate historical information, and attrition of the sample due to death or loss of follow up.

Retrospective studies thus lack the necessary controls for internal and external validity.

Inspection of the following retrospective studies using large samples of more than one hundred subjects over a long time span, twenty to thirty five years (Hoppe-Hirsch *et al.,* 1990; Jannoun & Bloom, 1990; Jenkin *et al.,* 1998; Lannering *et al.,* 1990; Onoyama *et al.,* 1975; Syndikus *et al.,* 1994) illustrates the effects of attrition in which the samples are reduced in numbers due to death and being lost to follow up. Consequently, only a relatively small number of survivors are tested. The very large sample of over two hundred subjects of Jenkin *et al.,* (1998) was reduced to only 10% of the original sample. Jannoun & Bloom (1990) fared better as 33% of the sample were tested. Lannering *et al.,* (1990) attempted to overcome the attrition of their sample by extracting a sub group of half the subjects who were tested and compared their Quality of Life to a matched control group.

The cohort effects of designs over a long period of time are increased as the time span of the investigation lengthens. The year or decade in which a particular person was born may affect performance, suggesting that the developmental course of the particular cohort may differ from cohort groups born earlier or later. The retrospective study of Hetherington *et al.,* (2000) covered a thirty one year time span. The authors attempted to strengthen the validity of the design by introducing a control group matched approximately on age and socioeconomic status. The age factors are clearly illustrated but the SES factors are not detailed, which is a potential source of bias over such a long time span.

Prior to 1980 all the studies reviewed used retrospective descriptive designs and non parametric statistics.

6.3.2.2 Prospective Studies

Prospective designs provide more direct evidence of risk and are most valuable when specific hypotheses have been developed from previous retrospective studies. However prospective designs are time consuming, difficult to execute and are inefficient for studying rare attributes. They are also not suitable for exploratory research where the examiner wishes to look at a large number of factors of doubtful significance such as hydrocephalus, the presence of seizures or cerebellar mutism.

Nineteen or 30% of the studies reviewed are prospective studies.(Barr *et al.,* 1993; Billison Walker, 1994; Bordeaux *et al.,* 1983; Brookshire *et al.,* 1990; Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Hudson & Murdoch, 1992; Kao *et al.,* 1994; Kun *et al.,* 1983; Lazereff *et al.,* 1996; Mulhern & Kun, 1985; Mulhern *et al.,* 1989; Mulhern *et al.,* 1994; Packer *et al.,* 1989; Radcliffe *et al.,* 1992; Roux, 1987; Silber *et al.,* 1992; Sutton *et al.,* 1989; Whitton *et al.,* 1997).

Twelve or two thirds of the prospective studies, utilized repeated measures as a means of verifying the outcome results (Bordeaux *et al.,* 1988; Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Kao *et al.,* 1994; Kun *et al.,* 1983; Mulhern *et al.,* 1985; Mulhern *et al.,* 1989; Packer *et al.,* 1989; Radcliffe *et al.,* 1992; Silber *et al.,* 1992; Sutton *et al.,* 1989).

The advantages of repeated measures are that they provide critical data regarding the continuities or discontinuities related to the impact of acute and chronic processes as these interact with developmental factors (Achenbach in Ris & Noll, 1994). In addition each child acts as his or her own control.

A major disadvantage of repeated measures is the issue of practice effects. However given sufficient time between test administrations this may not be a confounding factor

6.3.3 Treatment Interaction Effects

The treatment effects of surgery, radiotherapy, chemotherapy and other medical interventions are difficult to extrapolate. The treatments used singly may affect cognitive status or may interact with RT to potentiate its effect (Duffner *et al.,* 1988). Longitudinal designs over at least four years are the best method of illustrating the effects of treatment on neuropsychological functioning and the outcome on quality of life (Fletcher and Copeland, 1988; Ris and Noll, 1994). As discussed six longitudinal studies were identified (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,* 1994; Kao *et al.,* 1994; Mulhern *et al.,* 1989; Radcliffe *et al.,* 1992).

6.3.4 Treatment Group Assignment

In most published studies the random assignment of subjects to treatment groups is rare. In research on survivors of children of posterior fossa brain tumours, subjects are self-selected into groups according to tumour types or treatment protocols. The problem of small sample size and extreme outlying scores are difficulties that bias compatibility between groups across all critical domains. Baseline testing is a means of establishing group equality, but is often not possible when ill children are being tested. Control groups are seldom ideal but provide an alternative to random allocation treatment group assignment.

6.3.5 Control Groups

According to Fletcher and Copeland (1988) in their review of CNS prophylaxis of treatment of cancer in children, there are no ideal contrast groups, but the inclusion of children with cancer who do not receive CNS treatment represents a minimal comparative condition. In the studies reviewed only nine studies (14%) used matched sibling or relatives as controls and one study used random adolescent controls (Bauld *et al.,* 1998; Hetherington *et al.,* 2000; Lannering *et al.,* 1990; Roux, 1987; Riva *et al.,* 1989; Mostow *et al.,* 1991; Noll *et al.,* 1994; Nishiyama *et al.,* 1994). All these studies are retrospective in design.

6.3.6 Statistical Analyses

Small sample size is a major constraint on the statistical power and the type of analysis used in the studies examined. Nineteen or 30% of the studies used descriptive statistics(Bamford *et al.,* 1976; Broadbent *et al.,* 1981; Chin *et al.,* 1984; Cohen *et al.,* 1993; ; Danoff *et al.,* 1982; Duffner *et al.,* 1983; Feeny *et al.,* 1993; Gajjar *et al.,* 1994; Hirsch *et al.,* 1979; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Jenkin *et al.,* 1998; Kimmings *et al.,* 1995; Le Baron *et al.,* 1988; Li *et al.,* 1984; Mulhern *et al.,* 1989; Nishiyama *et al.,* 1994; Onoyama *et al.,* 1975).

Twenty one or 33% of the studies used non parametric statistics.
(Barr *et al.,* 1993; Billison *et al.,*1994; Chadderton *et al.,* 1995; Chapman *et al., 1995;* Duffner *et al., 1988;* Eiser, 1981; Johnson *et al.,* 1994; Kao *et al., 1994;* Kun *et al.,* 1983; Lazareff and Castro-Sierra, 1996; Moore *et al., 1992;* Mulhern & Kun, 1985; Mulhern *et al.,* 1994; Packer *et al.,* 1989; Radcliffe *et al., 1992;* Roux, 1987; Seaver *et al.,* 1994; Silverman *et al.,* 1984; Sutton *et al.,* 1989; Whitton *et al.,* 1997; Yang *et al.,* 1997)

Twenty three or 37% of the studies used parametric procedures such as analysis of variance (Bauld *et al.,* 1998; Bordeaux *et al.,* 1988; Brookshire

et al., 1990; Dennis *et al.,* 1991; Dennis *et al.,* 1991; Dennis *et al.,* 1992; Dennis *et al.,* 1996; Dennis *et al.,* 1998; Ellenberg *et al.,* 1987;Grill *et al.,* 1999; Hetherington *et al.,* 1999; Jannoun & Bloom 1990; Jordan *et al.,* 1995; Lannering *et al.,* 1990; Moore *et al.,* 1994; Mostow *et al.,* 1991; Mulhern *et al.,* 1999; Noll *et al.,* 1999; Packer *et al.,* 1987; Riva *et al.,* 1989; Silber *et al.,* 1992; Syndikus *et al.,* 1994)

6.4 MEASUREMENT ISSUES RELATING TO NEURO-PSYCHOLOGICAL OUTCOME.

The measurement of neuropsychological outcome has ranged from general impressions of outcome to detailed studies of specific cognitive functions.

6.4.1 Psychometric Issues

A comprehensive neuropsychological battery of tests designed to measure specific domains is the ideal method of assessment (Mulhern, Armstrong & Thompson, 1998). This form of assessment has been done in 32% (20) of the articles reviewed (Bordeaux *et al.,* 1988; Brookshire *et al.,* 1990; Chadderton *et al.,* 1995; Chapman *et al.,* 1995; Packer *et al.,* 1987; Dennis, Spiegler, Fitz *et al.,* 1991; Dennis Spiegler, Hofman *et al.,* 1991; Dennis *et al.,* 1992; Grill *et al.,* 1999; Johnson *et al.,* 1994; Le Baron *et al.,* 1988; Mulhern and Kun 1985; Mulhern *et al.,* 1989; Moore *et al.,* 1992; Moore *et al.,* 1994; Packer *et al.,* 1987; Packer *et al.,* 1989; Seaver *et al.,* 1994; Sutton *et al.,* 1989)

As neuropathological investigations suggest that white matter and subcortical structures are more likely to be damaged by RT than the cortex (Crossen *et al.,* 1994; Price & Birdwell, 1978 in Mulhern, 1994), the use of IQ tests may not be the most sensitive measure to illustrate the impact of RT. None the less some authors relied only on IQ test scores as

the measure of assessment (Dennis *et al.,* 1996; Eiser, 1981; Gajjar *et al.,* 1994; Mulhern *et al.,* 1999; Silber *et al.,* 1992).

Mulhern *et al.,* (1999) showed that the IQ test scores illustrated the effects of treatment on intellectual functioning. Serial testing as a means of showing the child's cognitive response to treatment over a period of time was done by Silber *et al.,* (1992) who showed that the higher the dose of radiotherapy the greater the decline in FSIQ. However Gajjar *et al.,* (1994) found that IQ scores improved during chemotherapy but decreased over time when chemotherapy was terminated and radiotherapy treatment commenced. The use of IQ tests in these instances measured the deficits in intellectual functioning.

The use of different types of IQ tests to assess survivors over different ages may be problematic. Generally this was not discussed in the interpretation of the results (Brookshire *et al.,* 1990; Bordeaux *et al.,* 1983; Chadderton *et al.,* 1995; Dennis Spiegler Fitz *et al.,* 1991; Dennis, Spiegler, Hoffman *et al.,* 1991; Dennis *et al.,* 1992 Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Grill *et al.,* 1999; Johnson *et al.,* 1994; LeBaron *et al.,* 1988; Moore *et al.,* 1992; Packer *et al.,* 1989; Radcliffe *et al.,* 1992; Seaver *et al.,* 1994; Sutton *et al.,* 1989)

Silber *et al.,* (1992) are the only authors in the review who discussed the effect of eight different IQ test instruments to measure intellectual and developmental functioning. In their analysis of IQ change as a function of irradiation dose and age they found that change of testing instrument did not contribute significantly to outcome. Patients who had initially been tested using the WPPSI, Stanford Binet, McCarthy or Bayley measures and who were subsequently tested on the WISC, WISC-R, WAIS or WAIS-R were considered to have changed tests. This effect size was minus 4.3 points for those who had changed tests, which was not significantly different from zero. The authors then explored other models for the other IQ measures and adjusted the initial FSIQ downward by 2.5

and 5 IQ points when the measures changed in the younger patients from the WPPSI to the WISC-R. The coefficients on the initial FSIQ, age at irradiation and dose were almost identical between the adjusted and unadjusted models. The authors thus chose to report the unadjusted models for their analysis. One could thus postulate that although the use of different IQ tests may have some influence when pooling IQ scores across age ranges, the effect is not significant. It must be noted that when the authors reported in the summary of their study that they corrected for age at irradiation and initial IQ this was not deemed to be a result of using different IQ test measures. Rather the variation in initial IQ scores across patients was seen to be the most important predictor of future IQ score with a partial correlation of 39%. In the normal test, retest situation scores tend to fall within five points of each other. It is for this reason that the authors corrected the initial IQ scores.

6.5 NEUROPSYCHOLOGICAL DOMAINS OF OUTCOME

6.5.1. Intelligence

Impaired intelligence test scores are not present in survivors of all posterior fossa brain tumours but are predominant in survivors of medulloblastoma brain tumours (Dennis *et al.,* 1996; Duffner *et al.,* 1983; Grill *et al.,* 1999; Hirsch *et al.,* 1979; Hoppe-Hirsch *et al.,* 1990;Johnson *et al.,* 1994; Mostow *et al.,* 1991; Mulhern *et al.,* 1999; Packer *et al.,* 1987; Silverman *et al.,* 1984; Yang *et al.,* 1997) Children with other types of posterior fossa brain tumours, such as non malignant cerebellar astrocytoma brain tumour survivors not treated with radiotherapy, show non-significant changes in their IQ scores (Chadderton *et al.,* 1995; Mulhern *et al.,* 1999; Packer *et al.,* 1989; Sutton *et al.,* 1989). The type of posterior fossa tumour and the extent of the treatment are thus potentially confounding variables in the cognitive outcome of posterior fossa brain tumour survivors.

Several studies revealed that VIQ is significantly higher than PIQ in posterior fossa tumour survivors (Dennis *et al.,* 1996; Johnson *et al.,* 1994; Mulhern and Kun 1985; Moore and Copeland *et al.,* 1992; Packer *et al.,* 1989; Sutton *et al.,* 1989). However, Silverman *et al.,* (1984) reported no discrepancy and LeBaron *et al.,* (1988) found a slight discrepancies of not more than five points. Two studies in which pre- and post-operative IQ scores are available (Packer *et al.,* 1989; Sutton *et al.,* 1989) illustrated that the significant difference between VIQ and PIQ not only appeared in the medulloblastoma group but also in the control astrocytoma group. Implying that the site of the tumour is a possible contributing factor to the outcome.

Dennis *et al.,* (1996) attempted to clarify the issue in a sample of medulloblastoma children, and demonstrated that PIQ was related to chronological age at which tumour diagnosis was made, whereas VIQ increased with time elapsed since treatment, being less dependent on the stage of development at which the tumour was diagnosed.

6.5.2. Attention

Problems with selective attending and excessive distractibility during neuropsychological testing were identified by Mulhern and Kun (1985) in younger children with no consistent influence for gender, increased intracranial pressure, tumour site, irradiation treatment or sensorimotor impairment. Small patient numbers preclude Kun *et al.,* (1983) from identifying the specific aetiologies of attentional difficulties in their sample. Problems with cognitive flexibility and problem-solving skills were noted by LeBaron *et al.,* (1988). They were unable to clarify if the difficulty was related to age, tumour type or treatment.

Riva, Pantaleoni, Malani, *et al.,* (1989) proposed that tumour or surgically-related disturbance of the reticular activating system was the common mechanism for the observed difficulties found on the attentional tests of

TMT A and B and the computer administered Continuous Performance Test. They found that different tests measured different parameters of attention showing that some aspects of attention are not affected by treatment.

Moore, Ater *et al.,* (1992) reported that the mean freedom from distractibility score of the no-radiation group of brain tumour children was significantly better than the radiated brain tumour group. A significant negative correlation occurred between the time after cranial irradiation and the attention domain suggesting that the deficit became more pronounced with time.

Dennis *et al.,* (1998) showed that survivors treated with RT performed less well than those treated without RT on both focused and selective attention tasks. Later age at onset of tumour symptoms correlated with a higher selective attention score whereas a shorter Time-since-Treatment correlated with a higher focused and selective attention scores.

Survivors of different kinds of cancer other than brain tumours and treated with intrathecacal chemotherapy, cranial RT and no cranial RT, were assessed by event-related potentials and motor reaction time tests (Moore, Copeland *et al.,* 1992). Mean reaction time and P300 latency were slower in the group given intrathecal chemotherapy relative to the group who received no CNS treatment. Significantly delayed reaction times were shown in the cranial RT group and correlations were shown with neuropsychological results. The authors conclude that the slowing of cortical activity secondary to white matter damage may underlie the cognitive decline in children treated with intensive CNS therapy, especially cranial RT.

In summary deficits in attention may well underlie impairments in cognitive functioning found in children with posterior fossa tumour tumours.

6.5.3 Speech and Language

Since the beginning of the 20th century it has been documented that cerebellar lesions induce speech deficits. These were thought to result from lack of motor coordination to the muscular activity needed for phonation (Molinari, Leggio, Silveri, 1997; in Schmahmann, 1997).

Jordan, Murdoch, Buttesworth *et al.,* (1995) found that language functions in three different brain injured groups (posterior fossa brain tumours, ALL and severe closed head injuries) were all compromised when compared to the control groups. However specific language deficits were not found in any of the brain injured groups. Scores obtained on Listening Quotient, Speaking Quotient, Boston Naming Test and Word Association subtest of clinical evaluation show that the groups did not differ from each other despite the varying underlying pathologies. Motor speech impairment was absent, except for only two of the posterior fossa tumour subjects demonstrating speech difficulty. The authors postulate that the similarities in deficits of the three brain-injured groups indicated that the language deficits were secondary to the primary injury. The common denominator in all the groups therefore is some degree of diffuse brain injury with or without concomitant focal lesions.

Bordeaux *et al.,* (1988) reported deficits in rapid word retrieval under time constraints at baseline testing. The authors suggested that the deficits shown in the children with a variety of brain tumours, were due to tumour related effects and/or secondary effects of hydrocephalus, cranial nerve palsies or systemic medication, rather than treatment, as there was little difference in the scores from pre- to post-treatment.

Significant language impairment was not found in children treated for malignant or benign brain tumours located predominantly in the posterior fossa (Brookshire *et al.,* 1990; Moore *et al.,* 1992; Packer *et al.,* 1989). However, a slight increase in language difficulties occurred two years after treatment according to Packer *et al.,* (1989). The authors argued against an age effect being responsible for the preservation of language abilities and proposed a hypothesis that dominant hemisphere functions are relatively less vulnerable to the effects of cranial RT than non-dominant hemisphere functions.

Johnson *et al.,* (1994) maintain that verbal fluency was moderately to severely impaired in only four cases or 31% of long term survivors treated for medulloblastoma brain tumours.

Hudson and Murdoch, (1992) discerned changes in language abilities of three children treated for medulloblastoma tumours and monitored over a period of 28 months. The presence of residual language deficits was hypothesized as being a possible but not an inevitable outcome. Severe semantic-lexical deficits detected immediately post-treatment improved dramatically in the first six months after treatment The authors speculated that as none of the language difficulties were present prior to surgery, they could not be attributed to the direct effects of the tumour. Age and the effects of raised intracranial pressure as possible contributing factors were also discounted. Structural and functional changes in the cerebrum as a result of exposure to the effects of radiation treatment, are offered as a possible explanation of the language disturbance. The small sample size is a major constraint on the interpretation of these results.

A marked drop in verbal comprehension scores was identified by Grill *et al.,* (1999) in children who had received higher doses of radiation treatment.

In summary, some language and verbal difficulties were identified by various authors. It is difficult to extrapolate the reasons for these difficulties as small sample size, the retrospective nature of the designs, variable age at diagnosis and time since treatment are potential confounding factors in the interpretation of the results. Grill *et al.,* (1999) are the only authors to have shown that lower verbal comprehension scores are due to high doses of radiation treatment in posterior fossa tumour subjects.

6.5.4 Visual Perceptual Information Processing

Visuomotor integration, fine motor speed and dexterity difficulties were documented following treatment of RT and chemotherapy for posterior fossa brain tumours (Hoppe-Hirsch *et al.,* 1995; Packer *et al.,* 1987; Packer *et al.,* 1989).

Prior to treatment Brookshire *et al.,* (1990) showed that the mean visual motor scores of a group of children with primary brain tumours were slightly lower than the mean scores in other neuropsychological domains. However, when the patients were grouped according to tumour location, 73% of the infratentorial tumour group performed within or above the normal limits.

The visual spatial scores for a group of children, diagnosed with cancer other than brain tumours, were decreased according to the intensity of the treatment received (Moore, Copeland *et al.,* 1992). The visual spatial skills were measured by means of Visual Motor Integration Tests and Block Design subtest of Wechsler Intelligence Scale for Children – Revised.

In another study on children with tumours of various types diagnosed during infancy, mean scores for the children in the no RT group were significantly below age-based normative means. The RT group scored

significantly lower in visual perceptual skills than the no RT group (Moore, Ater *et al.,* 1992). On the other hand Johnson *et al.,* (1994) found that perceptual organization was moderately to severely impaired in 23% of the sample of subjects treated for medulloblastoma brain tumours. When motor skills were also required, the incidence of impairment increased to 54% of the subjects.

In summary visuomotor integration, fine motor speed and dexterity deficits are documented both at baseline testing and following treatment in survivors of posterior fossa tumours. Treatment-related effects on functioning are variable.

6.5.5 Memory

In the domain of memory deficits or the lack thereof are not often reported. Difficulties in verbal memory were found in younger but not older children in a sample of those treated for tumours of various sites by Mulhern and Kun (1985).

Packer *et al.,* (1987) showed that only 33% of a sample of long-term survivors of medulloblstoma tumours had deficits in verbal memory after RT. Assessment before and after receiving RT showed no significant changes in verbal memory modalities in a sample of children diagnosed with brain tumours of various origins by Bordeaux *et al.,* (1988).

Sutton *et al.,* (1989) showed that memory functions were normal at baseline testing in both the medulloblastoma and astrocytoma brain tumour groups. Two years post RT the memory scores fell into the mild to moderate range of dysfunction in 38% of the children in the group treated with RT, particularly among those under seven years old at time of treatment.

A greater proportion of survivors of medulloblastoma brain tumour subjects, indicated moderate to severe deficits in visual memory as opposed to verbal memory according to Johnson *et al.*, (1994).

Dennis, Spiegler, Hoffman *et al.,* (1991) in a complex study, demonstrated that memory impairment was present in their entire sample of children and adolescents diagnosed and treated for brain tumours of various types. Verbal intelligence accounted for less than one quarter of the variance in scores. Working memory and memory for semantically based word picture associations were unaffected by Age-at-Diagnosis, Time-from-Treatment to testing, sex, pre-tumour developmental disturbances, closed head injury, post-tumour anticonvulsant treatment and post-tumour seizures. Memory for serial order of pictures that corresponded with heard words varied inversely with Age-at-Diagnosis. The older the subject, the lower the memory test score.

Dennis, Spiegler, Fitz *et al.,* (1991) elaborated on the memory tasks, finding that memory for semantically-based word picture associations was unaffected by tumour location. They postulated that memory for serial order pictures that corresponded with the heard words involved structures in the limbic and hypothalamic pituitary axis. However, working memory, in which a succession of heard words is stored in temporary memory long enough to be compared and contrasted with incoming words, involved the pineal region and anterior and medial thalamic nuclei.

Dennis, Spiegler, Obonsawin *et al.,* (1992) explored the effects of radiation on memory and showed that memory for word meaning was not associated with either RT history or hormone status. Severe deficits in working memory were associated with a history of RT and principle tumour site that involved thalamic epithalamic regions. Severe deficits also occurred in serial position memory associated with impaired hormone function and older age at tumour diagnosis.

Dennis *et al.,* (1998) reviewed working memory in children treated for various brain tumours with and without RT in the chronic phase of recovery. The mean percentile scores were within the normal range. However 41% percent of the sample scored within the lowest quarter of percentile distribution. The RT effects were more pronounced in the posterior third ventricle tumour group and the fourth ventricle group but neither Age-at-Diagnosis nor Time-since-Treatment correlated with working memory deficits.

Dennis *et al.,* (1998) also tested implicit memory in a sample of adolescents treated for brain tumours of the third ventricle and brain stem and matched to controls. Both the tumour group and the controls had a high level of explicit recognition. Unexpectedly, the tumour group revealed perfect explicit recognition less often than the control group under conditions of divided but not full attention, although the tumour group showed less priming than the controls when they were treated under either full or divided attention. Age-at-Diagnosis did not affect performance. The authors considered that the tumour group needed less priming than the controls, as they benefited less from exposed material, even material to which they did not attend consciously.

In summary working memory is influenced by tumour site, type and treatment and is worse in third ventricle and fourth ventricle posterior fossa tumour subjects. Visual memory is not often assessed but was found to be defective in medulloblastoma tumour survivors. Verbal memory scores were variable and were related to Age-at-Diagnosis, type of tumour and hormonal effects.

6.5.6 Motor Functions

Impairment in motor functions in survivors of posterior fossa tumours are reported by several authors. This is not surprising given the site of the

tumour. Brookshire *et al.,* (1990) found poor motor functions prior to treatment and Bordeaux *et al.,* (1988), Johnson *et al.,* (1994), LeBaron *et al.*, 1988, Packer *et al.,* (1987)) described impairment in motor functions after treatment. These authors attributed the impairment to the effects of the site of the tumour.

Moore Ater *et al.,* (1992) suggested that the combination of young Age at Diagnosis and cranial RT had a significant detrimental effect on motor functions.

However the implication of Time since treatment on motor functions is variable. Hoppe-Hirsch *et al.,* (1990), Hoppe-Hirsch *et al.,* (1995) and Packer *et al.,* (1989) showed that motor skills did not deteriorate with Time-since-Treatment. Whereas Lannering *et al.,* (1990) showed that despite normal motor functioning on neurological examination, Stott's test revealed a definite motor problem in the ability to balance.

Johnson *et al.,* (1994) indicated that medulloblastoma survivors who did not undergo shunting performed worse with both the preferred hand and the non-preferred hand than those who had shunts.

Variable findings are thus shown in the domain of motor functions. These findings are associated with the effects of the tumour, treatment, Age-at-Diagnosis, time-since-Treatment and shunts.

6.6 THE MEASUREMENT OF OUTCOME PERTAINING TO QUALITY OF LIFE ISSUES.

6.6.1 Quality of Survival versus Quality of Life

In early studies of brain tumour survivors gross quality of life measures did not predict psychometric or educational outcome and researchers were more concerned about issues relating to Quality of Survival (Onoyana *et*

al., 1975) rather than Quality of Life. This was completed without the use of norm referred tests and involved an analysis of school performance or placement, the presence or absence of mental retardation or a global assessment of daily functioning. There were two major classifications based on daily functioning: Bouchard's (1966) three levels of daily functioning and Bloom *et al.,* (1969) four categories of functioning. The Bloom rating scale, in conjunction with an intelligence test, is still being used in the literature to give levels of function applicable to daily living (Ellenberg *et al.,* 1987; Hirsch *et al.,* 1979; Jannoun & Bloom, 1990; Kun *et al.,* 1983; LeBaron *et al.,* 1988; Yang *et al.,* 1997).

As an index of global functioning Kun *et al.,* (1983) found that Bloom's criteria (four categories of disability from no disability, partial disability active life, partial disability capable of self care to total disability, incapable of self care) provided information on gross survival characteristics, excluding detailed psychological analysis. The authors noted that the 20% incidence of significant disabilities shown in their sample is almost identical to data from Bloom's initial medulloblastoma report and other reviews of childhood brain tumours.

Ellenberg *et al.,* (1987) estimated significant functional difficulties in almost 50% of the sample of subjects with brain tumours. This is higher than that obtained by Bloom *et al.,* (1969) who rated 30% of the sample as slow learners and 18% as being in category 111 or 1V. Ellenberg surmises that the discrepancy in findings could be due to the inclusion of all patients and not just long-term survivors, as patients who are more severely affected have a poorer long-term prognosis. Alternatively, it maybe that the thorough neuropsychological battery uncovered disabilities not apparent in less detailed studies.

LeBaron *et al.,* (1988) found that both global quality of life ratings and specific neuropsychological testing are necessary to uncover the severity of and range of deficits.

The Bloom criteria were specifically utilized as a quality of life rating and discussed and compared to the FSIQ findings according to tumour location, site of maximum RT dose and Age-at-Treatment by Jannoun and Bloom (1990). Quality of Life was better in the infratentorial brain tumours survivors than the supratentorial brain tumours survivors. Quality of life according to Bloom criteria supported the FSIQ outcome scores showing that the older the Age-at-Treatment the better one's quality of life. In summary the authors conclude that three to twenty years after receiving treatment for brain tumours 60% of the patients are functioning in the average range of intelligence or higher and about 57% of them are leading normal lives without any neurological or physical disability.

Of note in the articles is the assessment of both cognitive outcome and functional outcome. However, emotional, behavioural and scholastic functioning have not been well investigated. As will be seen in the rest of the review, these are ongoing domains of difficulty which have emerged in the discussions on Quality of Life in the 1990's.

6.6.2 School Performance

School failure is prevalent in children treated for posterior fossa brain tumours and approximately 74% of children treated for medulloblastoma tumours experience academic failure or report learning difficulties (Hirsch *et al.,* 1979), a rate which does not appear to have decreased in the intervening years (Johnson *et al.,* 1994). The incidence is not as high for survivors of cerebellar astrocytoma brain tumours (Hirsch *et al.,* 1979; Sutton *et al.,* 1989)

Special education arrangements are often required following RT and additional chemotherapy treatment as reported by several researchers (Chadderton *et al.,* 1995; Duffner *et al.,* 1988; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Packer *et al.,* 1989; Yang *et al.,* 1997).

Several studies indicated that treatment which did not include chemotherapy, but included surgery and RT, compromised school performance, resulting in learning problems which need remedial help or placement in a special school (Grill *et al.,* 1999; LeBaron *et al.,* 1988; Hoppe-Hirsch *et al.,* 1995; Jenkin *et al.,* 1998; Packer *et al.,* 1989; Sutton *et al.,* 1989).

Young Age-at-Diagnosis was found to have a negative influence on the development of learning problems at school (Chin & Maruyama, 1984; Johnson *et al.,* 1994). Many children treated at a young age have special educational requirements, although what is meant by "young age" is a debatable issue among the various researchers. Sutton *et al.,* (1989) suggested that children of between the age of eight years and ten years, or who have attained greater CNS maturation may have no serious learning difficulties.

Learning problems cited by several authors (Johnson *et al.,* 1994; Packer *et al.,* 1989; Packer *et al.,* 1987; Seaver *et al.,* 1994; Sutton *et al.,* 1989) in survivors of posterior fossa brain tumours include problems in maths, arithmetic, reading and spelling.

Grill *et al.,* (1999) showed that poor academic progress was due to high doses of cranio spinal irradiation treatment.

Yang *et al.,* (1997) document the Taiwan experience of a group of children with medulloblastomas brain tumours. He showed that there was a significant positive correlation between academic achievement and

intellectual performance, although no significant correlation was observed between functional status and intellectual performance.

In summary the incidence of school failure is higher in children treated for medulloblastoma tumours with adjuvant treatment compared with astrocytoma survivors treated by surgery only. However high doses of craniospinal irradiation have a negative effect on school progress. Young Age-at-Diagnosis has a variable influence on learning problems and special education needs. The correlation between intellectual status and functional status is reported as not significant by one researcher, but needs further exploration.

6.6.3 Emotional And Behavioral Functioning

A high proportion of children treated for brain tumours may have chronic problems with emotional adjustment. According to Kun *et al.,* (1983) and Mulhern (1994) it is difficult to ascertain whether these problems are due primarily to the tumour and the subsequent treatment affecting the CNS directly, making the child more vulnerable to stress. Alternatively these may be secondary difficulties of the tumour and treatment in which children have difficulty in adapting to the functional limitations imposed by the tumour and treatment. Estimates of clinical maladjustment have been at rated as at least 50% by Mulhern and Kun, (1985) and LeBaron *et al.,* (1988)

Seaver *et al.,* (1994) found no evidence of psychosocial difficulties where as Lannering *et al.,* (1990) rated psychological-emotional sequelae as having a heavier impact on the patients' lives than functional motor impairment.

According to Bauld, Anderson and Arnold (1998), no single predictor of psychosocial outcome has been identified in the adjustment of cancer survivors (predominately ALL subjects). The complex interaction of

factors which seem to play a role in the adjustment of cancer survivors makes it difficult to determine those who are at greatest risk for psychosocial problems. In their sample of adolescent survivors there was no evidence of overt psychological impairment compared with healthy controls. The authors suggest that time has healed some psychological difficulties, but health professionals need to be aware of both overt and covert psychological scars.

Hoppe-Hirsch *et al.,* (1995) described an increase in the incidence of behavioural problems such as emotional regression, inhibition, slowness, negative attitude, instability and attention difficulties, in survivors of medulloblastoma but not ependymoma brain tumours, with increasing time. At the initial assessment one to two years after treatment, about 20% of the children in each tumour group were affected. The percentage remained stable in the ependymoma group, at the five and ten year post-treatment assessments. However, in the medulloblastoma group, the percentage of disorders increased to 40% and 56% at five and ten year post-treatment assessments. Specific details as to how the ratings were calculated are not given.

In summary variable findings on emotional and behavioural functioning ranging from normal to problematic are reported in survivors. No single predictor can account for the findings but the interaction of tumour, treatment and Time-since-Treatment are hypothesized.

6.6.4 Quality Of Life In Oncology

As neuropsychological measures are themselves indicators of quality of life a more theoretically grounded assessment of health related quality of life including emotional and behavioural functioning in school and work related fields is necessary.

Health status, functional status and quality of life statements are often used interchangeably although this is not appropriate according to Jenney, Kane and Lurie (1995). In 1998, Jeeney argued that quality of life is a broad concept which includes aspects of health over and above medical issues such as education, standard of living, community and family life.

The World Health Organization (WHO, 1948) defined health as "a state of complete physical, mental and social well being and not merely the absence of disease or infirmity."

The term "health related quality of life" in the context of health usage, implies that illness can have a consequence in almost all domains of life and supports the WHO definition of health (Jenney *et al.,*1995; Rosenbaum *et al.,* 1990).

Child health has been defined as the ability to participate fully in developmentally appropriate activities and requires physical, psychological and social energy (Pantell & Lewis, 1987 in Rosenbaum *et al.,* 1990). Children, unlike adults, are developing and changing with time and any instrument used to measure health-related quality of life must be sensitive to these changes (Feeny, Furlong and Barr, 1998; Jenney *et al.,* 1995).

6.6.5 Functional Measures Used To Assess Health Status

Developmental measures, such as the Vineland Social Maturity Scales, which are targeted at functional assessment of neurological maturation, implicitly judge the quality of life of the child across functional domains such as personal-social and fine motor adaptive ability. Numerous measures suitable for health assessment include the Sickness Impact Profile, Medical Outcomes Study, Nottingham Health Profile and the Child Health and Illness Profile. In the evaluation of these measures, it is

evident that they have been developed for varying purposes such as clinical evaluation of function, survey data gathering, or disease-specific outcome evaluation (Rosenbaum *et al.,* 1990). Thus in evaluating the assessment of quality of life, goals and measurement need to be clarified.

Assessment of quality in life in patients with cancer has concentrated on adult patients and the most used instrument has been the Karnofsky score (Karnofsky *et al.,* 1948) which was not developed for use in the paediatric population despite the adaptations made, but to assess both adults and children. Children have a better long-term survival following treatment for cancer than adults and any instrument used to examine the issues faced by children should address long term questions bearing in mind the possibility of a cure. According to Jenney *et al.,* (1995) in a review of the issues relating to the development of a measure of health outcomes in survivors of childhood cancer the measure should:

- Be reliable, valid and responsive to changes in health status
- Be quick and easy to use, yet comprehensive
- Be able to identify specific issues for cancer patients yet be applicable to all children and adolescents of similar ages so that comparisons can be made with the general population
- Be interpretable by paediatric oncologists with an index of overall value in order to compare the outcome of groups of individuals
- Include principal domains of functioning such as, activity/ mobility, psychological well-being, social integration, comfort/pain, achievement of cognitive developmental expectations, fertility/sexual maturation, sensory functions and satisfaction with life should be included.

6.6.5.1 The Multiattribute Health Status Classification (MHSC)

The MHSC consists of three to five levels of function within seven attributes of: sensation, mobility, emotion, cognition, self-care, pain and fertility.

Independent ratings by clinicians using the MHSC indicate that brain tumour children on active treatment have a higher morbidity than children undergoing ALL, Wilms tumour or neuroblastoma treatment (Feeny, Furlong, Barr *et al.,* 1992).

Barr, Furlong, Dawson *et al.,* (1993) applied the MHSC to survivors of ALL. They reported that the overall morbidity was greater in those who had high risk disease rather than standard risk disease. Deficits in emotion and cognition were common but more prevalent in younger patients and showed a dose relationship to cranial irradiation.

Feeny, Leiper, Barr *et al.,* (1993) used the MHSC to follow up long-term survivors of childhood cancer. The results showed that ALL survivors have a greater morbidity than the general population in Great Britain. Of the All survivors, 7% had deficits in sensation compared with 1.9% of the children in Great Britain who suffer from disabilities in seeing, hearing or communication. Similarly, while 28% of the ALL children have deficits in emotion, only 2.1% of the British children have problems in behaviour. Of ALL survivors 39% had problems in cognition compared with 0.9% in the British population.

A 80% functional morbidity was found using the MHSC to assess adult survivors of brain tumours and there were frequent problems in hearing, speech, ambulation and dexterity (Whitton, Rhydderch, Furlong *et al.,* 1997). Doctors identified fewer health deficits in survivors of cancer than patients or parents. Survivors of neuroaxial tumours had lower scores than other diagnostic groups (Billson and Walker, 1994).

In summary the MHSC is the only available rating scale specifically suited to survivors of RT and chemotherapy treatment. If the goal of the assessment is to monitor functional changes in both children and adults, it is a useful tool (Jenney *et al.,* 1995).

6.7 CONCLUSION

The literature review has explored how neuropsychological function and quality of life are related to several critical variables.

- Some studies have suggested that patient characteristics such as Age-at-Diagnosis and treatment, tumour site and type are the major predictors of long term outcome, with evidence of the detrimental effect being suggested for young age and chemotherapy on top of RT and surgery.

- Impaired intelligence is predominant in survivors of medulloblastoma tumours, with some studies suggesting a greater effect on PIQ than VIQ. Some disease consequences may not be fully apparent for several years after treatment has been completed.

- The areas where most deficits have been noted are visuomotor integration, fine motor speed and dexterity.

- Speech and language functions tend to be relatively spared. However more in depth studies may detect subtle deficits.

- Working memory and visual memory have been found to be sensitive to posterior fossa tumours, while findings are variable on verbal memory.

- Although both cognitive and health outcomes have been well investigated emotional, behavioural and scholastic functioning have not been well documented.

CHAPTER 7

METHOD

7.1. SAMPLE

7.1.1. Collection

The sample was collected by examining the records, from 1968 to 1996, of all children under the age of 17 years 11 months, admitted to Red Cross War Memorial Children's Hospital and Groote Schuur Hospital with a diagnosis of posterior fossa brain tumour.

- 174 such cases were found.

7.1.2. Diagnosis

The type of posterior fossa tumour was determined by histology. In the absence of surgery, the diagnosis was determined by CT Scan or MRI.

- 76.4% (133) of the tumours were diagnosed by means of histology.
- 23.5% (41) of the tumours were diagnosed on CT Scan or MRI. The majority of these tumours were brain stem gliomas.

7.1.3. Incidence of Tumour Types

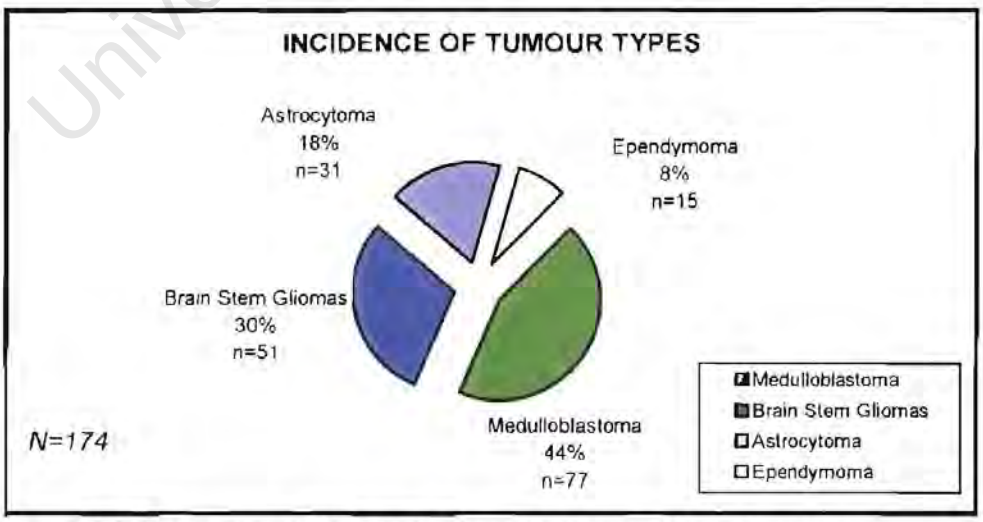


Figure 7-1 *Incidence of Paediatric Posterior Fossa Brain Tumours*

7.1.4. Mortality

An intensive tracing system was set up using the services of community health workers, clinic sisters, schools, work places and the Department of Deaths to determine which patients died and those which survived.

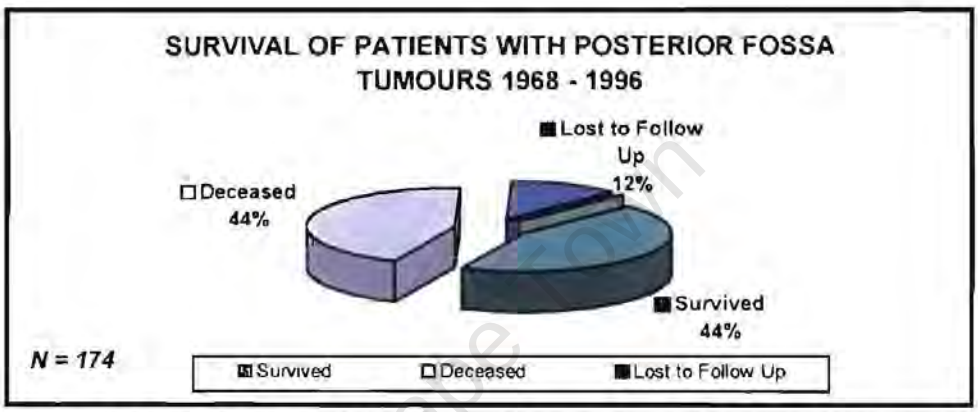


Figure 7-2 *Incidence of Survived, Deceased and Lost to Follow Up Patients*

The Lost to Follow Up Children, 12 % (21), could not be traced at the addresses given and no one in the neighbourhood could supply any information regarding their whereabouts. Of those that could be traced, there was an equal split between survivors (n=77) and deceased (n=76).

Table 7-1 *Description of Availability of Sample*

TESTED *n=51*	51 subjects or their parents gave consent to participating in the study
UNTESTED *n=26*	17 subjects resided in other provinces and were inaccessible. 6 subjects failed to keep their appointments despite repeated efforts to contact them. 2 children did not fit the treatment criteria which included surgery. A brain stem glioma (radiotherapy and chemotherapy only) and a medulloblatoma (radiotherapy only). 1 parent refused to participate.

7.2. INCIDENCE OF TUMOUR TYPES AS PER GROUP

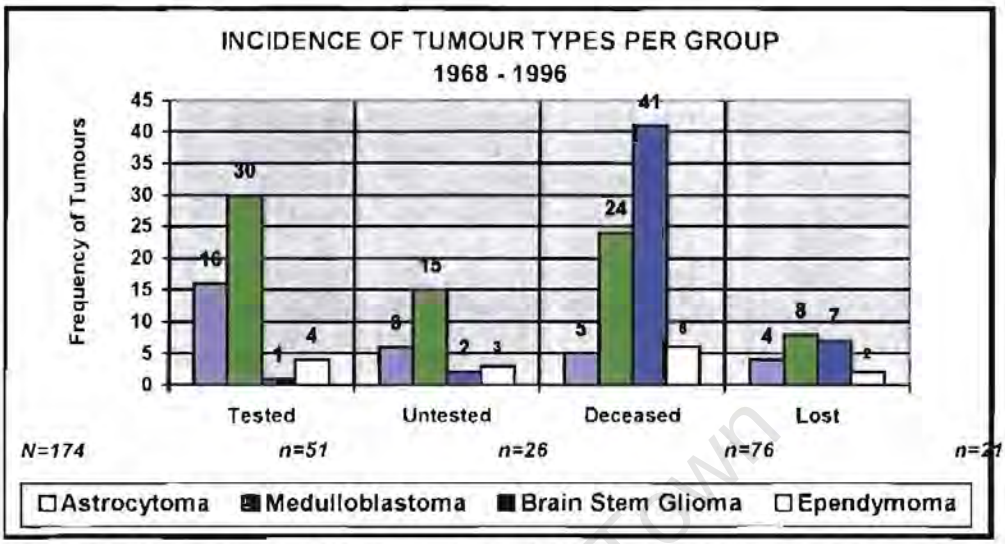


Figure 7-3 Incidence *of Tumour Types in Tested and Untested Subjects*

This figure shows that the deceased sample has an increased proportion of Brain Stem Gliomas (54%) but that the tested sample is representative of the survivors in terms of tumour type.

7.3. TREATMENT GROUPS

Criteria for inclusion in the study:

- Confirmation of diagnosis by histology
- No evidence of tumour recurrence
- The treatment had to include surgery

In accordance with the research design the tested sample (51 cases) were divided into three treatment groups according to the categories of treatment administered:

Group 1 Surgery only (n=12).

Group 2:Surgery and Radiotherapy (n=20)

Group 3:Surgery, Radiotherapy and Chemotherapy (n=19)

7.4. DEMOGRAPHY

Table 7-2 *Observed Frequencies of Gender, Race and Language .*

	GROUP 1 (n=12)	GROUP 2 (n=20)	GROUP 3 (n=19)	ALL GROUPS (n=51)
GENDER				
Male	3 (25%)	10 (50%)	11 (58%)	24 (47%)
Female	9 (75%)	10 (50%)	8 (42%)	27 (53%)
RACE				
Coloured	8 (67%)	14 (70%)	15 (79%)	37 (73%)
White	4 (33%)	5 (25%)	2 (11%)	11 (21%)
Black	0	1 (5%)	2 (11%)	3 (6%)
LANGUAGE				
English	9 (75%)	6 (30%)	9 (47%)	24 (47%)
Afrikaans	3 (25%)	13 (65%)	8 (42%)	24 (47%)
Xhosa	0	1 (5%)	2 (11%)	3 (6%)

7.4.1. Gender

There is no significant difference between the treatment groups in terms of gender (Pearson Chi Square = 3.309, df = 2; p=.19123).

7.4.2. Race

There are no significant differences between the treatment groups in terms of race (Pearson Chi Square = 3.565; df=4; p=.46812). In terms of the population of the Western Cape: (Central Statistics of the Western Cape Province,1995, in Central Statistics 1996), the White group is adequately represented (21.5% of the sample versus 23.8% of the population), the Coloured group is over-represented (72.5% within the sample versus 57.1% of the population), while the Black group is underrepresented (5.8% within the sample versus 18.2% in the population)

7.4.3. Language

There are no significant differences between the groups in terms of language (Peason Chi Square = 7.365; df=4; p=.11783). As shown by the Population Census (1991) of the Western Cape (Central Statistics 1996), Afrikaans is the predominant language (62.2% in the population versus 47% in the sample); English speakers are over represented in the sample (20.05% in the population versus 47% in the sample); Xhosa speakers are under-represented (15.3% in the population versus 5.8% in the sample).

7.4.4. Marital Status

Although the retrospective study covers a time span of 28.5 years, only three subjects are married or cohabiting with a partner. However the number of single parents is shown in the Psychosocial Adversity table.

7.5. AGE AND YEARS- SINCE- TREATMENT

Table 7-3 Age-*at-Diagnosis, Age-at-Testing and Years-since-Treatment, Expressed in Years*

	GROUP 1 (n=12)	GROUP 2 (n=20)	GROUP 3 (n=19)	ALL GROUPS (n=51)
AGE- AT- DIAGNOSIS				
X	6.74	7.93	7.68	7.56
SD	3.56	4.64	4.81	4.42
Range	1.33 – 14.5	1.6 – 17.1	0.9 – 17.2	0.9 – 17.2
AGE- AT- TESTING				
X	11.38	20.07	15.29	16.24
SD	4.84	11.34	8.24	9.50
Range	4.8 – 17	4.1 – 42.5	3.7 – 39.8	4.1 – 42.5
YEARS- SINCE- TREATMENT				
X	4.25	11.96	7.57	8.51
SD	4.63	9.29	5.92	7.72
Range	1.7 – 15	0.5 – 28.5	0.25 – 22.8	0.25 – 28.5

7.5.1. Age-at-Diagnosis

There are no significant differences between the treatment groups in Age-at-Diagnosis (Anova F=.275; df=2.48; p=.760).

7.5.2. Age- at-Testing

There is a statistically significant difference between the treatment groups in Age-at-Testing according to the Analysis of Variance (F=3.630; df=2.48; p=.034) where Group 1 (surgery) has the youngest children and Group 2 (S+RT) has the oldest subjects. An attempt has been made to control these possible confounding factors by using age-appropriate psychometric tests and age-related norms.

7.5.3. Years-since-Treatment

There is a statistically significant difference in the total sample in terms of Years-since-Treatment according to the Analysis of Variance (F=4.529; df=2.48; p=.015). The interaction between these variables is explored later.

7.6. OCCUPATION AS A MEASURE OF SOCIO-ECONOMIC STATUS

Occupational status was classified according to the breadwinner of the family. Where that person was not in current employment, his/her most recent occupation was taken as a criterion. Occupation was ranked according to the Centre for Applied Social Sciences (Schlemmer, Stopforth and Bulteel, 1979). There are five broad categories from professional to unskilled and menial class. An overview of the criteria for ranking occupational status for the group is shown in Appendix B.

Table 7-4 *Summary of Percentages Ranked in order according to Occupational Status in Treatment Groups.*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
Professional & Managerial	17% (2)	10% (2)	10% (2)	12% (6)
Middle White Collar	17% (2)	35% (7)	16% (3)	24% (12)
Manual Foreman & Skilled	42% (5)	20% (4)	42% (8)	33% (17)
Routine Non Manual	17% (2)	20% (4)	26% (5)	21% (11)
Unskilled Manual & Menial	8% (1)	15% (3)	5% (1)	10% (5)

There are no significant differences between the treatment groups according to occupational status (Pearson Chi Square=5.25,df=8;p=.073).

7.7. PSYCHOSOCIAL ADVERSITY

The distribution of various psychosocial adversity factors within the groups is summarized below. In rounded percentages a psychosocial adversity score was calculated for each child, based on one point for the presence of each of the factors (Hemp, 1989).

Table 7-5 *PSYCHOSOCIAL ADVERSITY*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
Large Family Size	0% (0)	15% (3)	1% (2)	10% (5)
Overcrowding	8% (1)	15% (3)	1% (2)	12% (6)
Unskilled/ Unemployed	25% (3)	50% (10)	37% (7)	39% (20)
Maternal Education < Std 6	33% (4)	40% (8)	47% (9)	41% (21)
Mother Psychiatric	8% (1)	0% (0)	5% (1)	4% (2)
Father Psychiatric	0% (0)	15% (3)	11% (2)	10% (5)
Single Parent	25% (3)	30% (6)	47% (9)	35% (18)
Disharmony in home	0% (0)	10% (2)	16% (3)	10% (5)
Ill health either parent	0% (0)	0% (0)	0% (0)	0% (0)
Nutrition	8% (1)	30% (6)	26% (5)	24% (12)
	Median Psychosocial Adversity Score			
	1	2	2	1.8

This table shows that there is a high incidence of mothers who have less than standard 6 level of education and are single parents. The unskilled and unemployment incidence reflects the present economic climate in which retrenchment and unemployment figures in the country are high. According a report in the Cape Times, 74,000 jobs are expected to be shed by the year 2003 (Nxumalo F, 1999).

7.8. MEDICAL VARIABLES

The history was established by medical folder review and patient/parent interview. As proposed by Mulhern *et al.,* (1998), all medical variables regarding pre-treatment, treatment and post-treatment were assessed. In addition a detailed pre-natal, developmental, scholastic and occupational history was recorded for each subject (see Appendix E).

7.8.1. Tumour Type As Per Treatment Group

Table 7-6 *Tumour Types as per Group*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19
Astrocytoma	100% (12)	20% (4)	-
Medulloblastoma	-	55% (11)	100% (19)
Ependymoma	-	20% (4)	-
Brain Stem Glioma	-	5% (1)	-

In Group 1 the tumours are diagnosed as non-malignant astrocytomas whereas those in Group 3 are malignant medulloblastomas. Group 2 comprises a mixture of different types of posterior fossa tumours; astrocytoma, medulloblastoma, ependymoma and brain stem glioma, all graded as malignant brain tumours. See Appendix A for histological diagnosis of tumours.

7.8.2. Presenting Symptoms

The signs and symptoms of posterior fossa tumours were grouped according to the criteria of Halperin *et al., (*1994):

- The pressure syndrome which presents as vomiting, lethargy/headache and/or papilloedema due to an increase in intracranial pressure from obstruction to the flow of the cerebral spinal fluid

- The cerebellar syndrome which presents as ataxia and/or difficulty in handling objects, due to interference with function in the local area of the cerebellum

- Seizures are uncommon as presenting symptoms in posterior fossa subjects.

Table 7-7 *Presenting Symptoms expressed as Percentages*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19
Duration of P/S	11 Weeks	11 Weeks	9 Weeks
Range	1 – 52 Weeks	1 – 52 Weeks	1 – 52 Weeks
Pressure - H/L	92% (11)	70% (14)	68% (13)
V	50% (6)	80% (16)	79% (15)
P	25% (3)	30% (6)	42% (8)
Cranial	33%(4)	50% (10)	42% (8)
Cerebellar	67% (8)	75% (15)	95% (18)
Seizures	8% (1)	0% (0)	11% (2)

n = 51

TABLE INDEX

P/S = Presenting Symptoms H/L= Headache/Lethargy V = Vomiting

P = Papilloedema Cranial= cranial nerve palsy

The mean duration of presenting symptoms is shortest in Group 3, which comprises medulloblastomas.

- Pressure symptoms: headaches and lethargy were common to all groups. Papilloedema occurred most frequently in Group 3, the medulloblastoma group. Cranial palsies occurred in almost half the subjects with sixth cranial nerve palsy being the most frequent.

- Cerebellar signs were common in all the groups but showed an upward trend from Group 1 to Group 3.

- Seizures: only three children presented with seizures.

7.8.3. Surgical Intervention

Surgery was coded as total or subtotal according to the operation notes written by the neurosurgeon. Some neurosurgeons used the term partial surgical resection, which was coded as a subtotal resection. In the sample, there were no instances of only a biopsy of the tumour being performed.

The standard procedure in the Neurosurgery Department is to insert ventriculo peritoneal shunts prior to surgical resection of the tumour in children who present with signs of raised intracranial pressure.

Table 7-8 *Surgical Intervention, Shunts and/or EVD Expressed in Percentages.*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19
EXTENT OF SURGERY			
TOTAL	83% (10)	45% (9)	32% (6)
SUB TOTAL	17% (2)	55% (11)	68% (13)
SHUNT/EVD			
SHUNT	83% (10)	65% (13)	89% (17)
EVD	-	5% (1)	-
SHUNT + EVD	-	-	11% (2)

n=51

EVD = External Ventricular Drain

There is an inversion between Group 1 (only astrocytoma tumours) the majority of which were total surgical resections and Group 3 (only medulloblastoma tumours) the minority of which were total surgical resections.

The majority of the children needed shunting. In three children, external ventricular drains were inserted prior to the surgical resection of the tumour, and in two cases (Group 3) were later replaced with shunts.

7.8.4. Radiotherapy Treatment

Table 7-9 *Sites of Radiation and the Range of Radiation Doses Administered.*

	GROUP 2 n=20	GROUP 3 n=19
WHOLE BRAIN	23 – 54 Gy	20 – 40 Gy
SPINAL	20 – 48 Gy	14 – 42 Gy
POSTERIOR FOSSA	10 – 49 Gy	10 – 58 Gy
CRIB BOOST	32 Gy	24 – 32 Gy

As this is a retrospective research study of 28 years, during which time there have been many changes in RT regimes, the dosage of radiotherapy has not been taken into account in any of the statistical analyses. However, it was included for descriptive purposes (see Appendix A for details). All the children in Group 3 (100%) received craniospinal RT with a boost to the posterior fossa area, compared with 80% in Group 2. The remaining 20% in Group 2 received RT to the posterior fossa area only. A radiation boost to the cribriform plate was given to one child only in Group 2 but to four children in Group 3. Children in Group 3 thus received more RT than those in Group 2.

The average duration of radiotherapy was six weeks for children in Group 2 and seven weeks for the Group 3 children (Appendix A). They all completed their treatment protocols.

7.8.5 Chemotherapy

Chemotherapy protocols consisted of vincristine, CCNU, cisplatin, MOPP and other agents but no children were given methotrexate (see Appendix A for details). In all cases chemotherapy was commenced during RT, although in two cases this was interrupted due to neutopenia. In one case, the mother of a child became distressed at the length of the treatment and refused consent for further chemotherapy.

7.8.6. Intra-Operative and Post-Operative Complications

Table 7-10 *Summary of Frequency of Intra-Operative and Post-Operative Complications*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
INTRA-OPERATIVE COMPLICATIONS				
	8% (1)	0%	5% (1)	4% (2)
POST-OPERATIVE COMPLICATIONS				
Infection	0%	15% (3)	26% (5)	16% (8)
Mutism	8% (1)	15% (3)	11% (2)	12% (6)
Seizures	8% (1)	0%	11% (2)	6% (3)
Total	25% (3)	30% (6)	53% (10)	

In the above table Intra-operative complications occurred in two children. A child in Group 1 (astrocytoma tumours only) developed episodes of hypotension which resulted in bilateral motor weakness, hypotonia and seizures. A case of airway obstruction occurred in a child in Group 3 (medulloblastoma tumours only) with the result that the operation was abandoned and rescheduled for a later date.

Post-operative infections included shunt infection and meningitis. Post-operative seizures necessitating medication and confirmed on electroencephalogram were found in 6% of the sample. Transient cerebellar mutism occurred in 12% (six cases) of the sample. The syndrome affected all tumour types, but was more prevalent in patients with medulloblastoma tumours (Group 2 = 1; Group 3 = 2). The vermis was the site of the tumour and hydrocephalus was present in all the children. The mutism was noticed in up to six days after the surgery and lasted from two to ten weeks. Cortical blindness in association with mutism developed in one child (Group 1) and was resolved within four days. The total incidence of complications showed an upward trend according to the addition of RT and chemotherapy treatment.

7.9. TEST BATTERY

7.9.1. Principles of Test Selection

- Measures of general ability and of specific neuropsychological functions were required for both adult and child survivors of brain tumours.

- As a result of the brain tumour and subsequent treatment, it was expected that many subjects would score below their age levels, so tests with a wide range and a low floor were selected. Tests with age norms were preferred. The intention was to make the test results comparable to those of other international studies.

- Tests which have been developed and validated using norms obtained in British and American population groups need to be interpreted with reserve (Anderson, 1998; Murdoch, Flemming, Skuy *et al.,* 1994). Therefore, use has been made of the South African Wechsler Adult Intelligence Scale (SAWAIS, 1962), the Senior South African Individual Scale Revised (SSAIS-R, 1991, 1991b) and the Individual Scale for Xhosa Speaking Pupils (ISX, 1988), which have been standardized according to the population predominating in this study.

- Tests should be repeatable, culture free and available.

- In the selection of the test battery an attempt was made to adhere to the Proposed Requirements for Practice Standards, Practice Guidelines and Practice Options in choosing psychological tests advocated by Mulhern *et al.,* see Appendix C.

7.9.1.1. Adjustment of Test Scores

- The SSAIS-R (1991) provides norms for the population of the non-environmentally as well as environmentally disadvantaged subjects with Afrikaans and English as their mother tongue. In order to apply the norms correctly, The Socio-Economic Deprivation Questionnaire, developed by the Human Science Research Council (Van Eeden, 1991 b), was applied to determine which set of norms should be used for each particular child. The environmentally disadvantaged norms were used in 13 cases. For the most part, these children were from the Coloured Community. Where only the mental age equivalents of scores were available, scores are expressed as age ratios (MA/CA x 100). Test scores are expressed as scale scores, percentiles or T scores.

7.9.2 Intelligence

- SAWAIS (16 cases, 18 years – 59 years)
- Verbal Subtests: Comprehension, Similarities, Digit Repetition
- Performance Subtests; Block Design, Digit Symbol Substitution (Coding)
- Subtotals prorated to give VIQ, PIQ and FSIQ

- SSAIS-R (22 cases, 7 years to 16 years 11 months)
- Verbal Subtests: Comprehension, Similarities, Story Memory, Digits
- Performance Subtests: Blocks, Coding
- Subtotal prorated to give VIQ, PIQ and FSIQ

- ISX (2 cases, 9 years to 19 years 11 months)
- Verbal Subtests: Comprehension, Similarities, Story Memory
- Performance Subtest: Blocks
- Additional Tests: Digits, Coding from SSAIS-R
- Subtotals prorated to give VIQ, PIQ and FSIQ

- The Griffiths Scales of Mental Development (1984), 8 cases (0- 8 years)
- Verbal Scale: Hearing and Speech

- Performance Scales: Hand and Eye Co-ordination, Performance Scale.
- VIQ =Mental age / chronological Age x 100
- PIQ = Mental age / chronological Age x 100
- FSIQ = mean mental age score of 5 scales: Speech and Hearing, Hand and Eye Co-ordination, Performance Scale, Practical Reasoning Scale. Mean mental age then transposed into GQ

SUBJECTS UNABLE TO DO ABOVE IQ TESTS (3 cases)

The Individual Scale of the National Bureau of Educational Research (1960) – Old South African Individual Scale (OSAIS).

- FSIQ = level of mental retardation

7.9.2.1. SAWAIS

The SAWAIS is based on the American Wechsler Adult Intelligence Scale and it was adapted for South African conditions and standardized on a South African norm group by the National Institute for Personnel Research (Liddicoat & Roberts, 1962; in Huysamen, 1996). Items specifically related to American conditions were rewritten to fit the South African context (Huysamen, 1996) the final standardization of the SAWAIS was in 1969. As it has not been revised since 1955, there is considerable criticism that the norms do not reflect the present day population (Nell, 1994) A means of maximizing the utility of the SAWAIS is for it to be part of a comprehensive neuropsychological evaluation which would include other tests covering functional abilities. (Adan 1986; Nell, 1994; Pieters & Louw, 1994 in Van Eeden, Robinson & Postuma, 1994).

Coetzee (1982, in Van Eeden *et al.,* 1994) finds that the verbal subtests of Comprehension and Similarities are good hold tests which are not affected by age, language or sex. Block Design and Coding are valid PIQ tests. All four subtests are good indicators of general intelligence. Coding is a good indicator of perceptual organization in a brain damaged population (Cohen, 1952 in Madge and Coetzee, 1982).

7.9.2.2 SSAIS-R

The SSAIS-R was developed from the original New South African Individual Scale (NSAIS,1964) which was renamed the Senior South African Individual Scale (SSAIS) in 1980. This scale was revised and normed from 1986 to 1988 on a sample of 2000 children, with English or Afrikaans as their mother tongue. The rank order correlation of the SSAIS-R total score, 0.44, with the index of socio-economic status, indicated that

environmental factors were partly responsible for the low scores obtained on the SSAIS-R. The HSRC therefore devised advantaged and environmentally-deprived norms based on a broader sample of 4,767 pupils which included both the advantaged and environmentally deprived subjects. This sample was a proportional representation of pupils extracted form school registers of the Tripartite Departments of Education.

The inter-correlations of all the subtests are high and show a common underlying factor which could be interpreted as "g" or general intelligence. Comprehension and Similarities form part of VIQ. Block design is a good indicator of PIQ. Coding does not form part of the composite scale as it had a loading of 0.40 and not 0.50 which was a criterion for inclusion. However, Picture Arrangement has the same loading and only after reconsideration was included by the test compilers in the composite scale (van Eeden & Visser, in van Eeden *et al.,* (1994). As Coding is a good indicator of visual perceptual dysfunction in a brain damaged population (Lezak, 1995) and in accordance with its inclusion in the SAWAIS in the testing of adults, it is part of the composite scale in the present study.

7.9.2.3. The ISX

The ISX was developed from the Indian Scale for South Africans which in turn was adapted from the New South African Scale, later know as the Senior South African Individual Scale (SSAIS). Norms were established from Xhosa speaking pupils age 9 to 19 years from schools in the Transkei and Ciskei of the Republic of South Africa.

In the development of the short form of the ISX, in which all the age groups were treated as one group, Blocks were shown to have the highest correlation of 0.72 with FSIQ (Landman, 1989, in Van Eeden *et al.*, 1994).

7.9.2.4. Griffiths Scales of Mental Development

The Griffith Scales were originally developed in Great Britain, for the assessment of children 0 to 8 years of age (Griffiths, 1984; Griffiths, 1986). The six scales, which make up the General Quotient are of equal difficulty for each age level:

A The Locomotor Scale assesses physical weakness.

B The Personal Social Scale gives an indication of personal and social development.

C The Hearing and Speech Scale is the most intellectual of all the scales assessing growth and development of language.

D The Eye and Hand Co-ordination Scale consists of items relating to handwork and visual ability.

E The Performance Scale measures skill in manipulation, speed of work and precision and is largely a performance test.

F The Practical Reasoning Scale depicts the earliest indication of numeric comprehension and practical problems.

The Griffiths Scales were introduced in South Africa in 1977 and have been well researched (Allan, Luiz, Foxcroft,1988; 1992; Luiz, Foxcroft, Sweeney, Kotras, 1997; Luiz, Foxcroft, Kotras, 1997; Luiz, Foxcroft, Stewart, 1998; Heimes, 1983; Krige, in Luiz,1997).

Heimes , find that the scales correlated well with the Junior South African Individual Scale (JSAIS). However Griffiths mean scores were higher than those of the JSAIS mean scores and this was consistent with other research (Ramsay & Fitzhardinge, 1977, in Van Eeden *et al.,* 1994).

A comparison of the performance of normal pre-school South African and British children on the Griffiths Scales by Allan *et al.,* (1988) indicates that when the South African sample of 1986 was compared with the original British sample of 1960, significant differences were found between the two groups. However, when the South African sample was compared with a later equivalent British age group sample, no significant differences were found. Allan *et al.,* (1988) suggest that a time factor rather than a cultural factor was responsible for the differences. The time factor was described as the changes that had taken place in the intervening years since the original sample were tested.

According to Allan *et al.,* (1992) an items analysis of the Griffiths scales demonstrated that the ethnic groups differed significantly in the percentage of items which they passed in each scale. The authors suggested that the British norms do not apply to South African White and Indian children but are more suited to South African Black and Coloured children.

Luiz, Foxcroft Stewart record significant correlations between the subscales of the Griffiths scales and the General Quotient for the White, Coloured, Indian and Black South African samples and the British standardized sample.

In the administration of the Griffiths scales, the locomotor scale was excluded as the children in this sample have motor difficulties and it was felt that these difficulties would bias the cognitive results. Specific tests of motor function were included in the battery. Luiz and Heimes (1988) found a high positive correlation between JSAIS GIQ and Griffiths GQ

when the locomotor scale was excluded. The personal social scale was also excluded as these items did not occur in intelligence tests. Heimes (1983) shows a high correlation between the JSAIS GIQ and the Griffiths GQ after the personal social scale was excluded. A possible limitation of the test is that there is only one sub scale for speech and language. None the less the scale incorporates the process of both encoding and decoding of language as the child is asked to name as well as define objects and includes comprehension questions.

7.9.3. Motor Functions

7.9.3.1. Speed and Co-ordination

Purdue Pegboard (Purdue Research Foundation, 1948)
The number of pegs correctly placed in 30 seconds using the preferred hand, non preferred hand and both hands are counted. Scores are then transformed into Percentiles using the norms in Spreen and Strauss (1991) for girls and boys and the normative data published by Gardner and Broman (1979) and Yeudall, Fromm, Reddon *et al.,* (1986) for adults. The use of the Purdue pegboard (Johnson *et al.,* 1994) and the grooved pegboard has demonstrated significant findings in an oncology setting (Chapman *et al.,* 1995; Mulhhern *et al.,* 1998).

7.9.3.2. Successive finger Taps (Denckla, 1973, 1974)

Time taken to do 20 successive finger taps, that is five sets of four, with the thumb moving from the index finger to the little finger just in the Preferred hand and then the Non preferred hand. The Denckla norms are guidelines based on small samples of children aged between ages of five to ten years and were supplemented by data collected locally at a particular Coloured school (Hemp, 1989)

Tests of manual dexterity are recommended by Mulhern *et al.,* (1998) whereas tests of fine motor co-ordination within an oncology setting are used by Bordeaux *et al.,* 1988; Brookshire *et al.,* (1990); Copeland, Dowell Jr, Fletcher *et al.,* (1988); LeBaron *et al.,* (1988); Packer *et al.,* (1989).

7.9.3.3. Balance (Denckla 1973, 1974)

The time for which balance on either the Preferred leg or the Non Preferred Leg can be maintained is recorded. In this instance Denckla norms are guidelines based on a small sample of children between five to ten years of age.

7.9.3.4. Gait

Ability of subject to walk on a two meter long straight chalk line. Ataxia was scored as present or not present. If gait was normal, the test was repeated with tandem walking which would confirm the presence of instability. Ataxic gait was included in battery by LeBaron *et al.,* (1988).

7.9.4. Attention

7.9.4.1 Trail Making A and B (norms of Spreen and Strausss, 1991).

TMT A is time taken to join consecutively numbered circles from 1 to 25 as quickly as possible. TMT B consists of double or a simultaneous tracking task and is considered to be more challenging. The subject must draw the lines alternating between numbers and letters as quickly as possible. Errors count only in the increased time of performance, as the examiner does not stop timing whilst the error is corrected.

TMT A and B are measures of attention, concentration, mental flexibility and speed under time constraints. A successful performance depends on intact visual perceptual motor ability. According to Lezak (1995), the test is sensitive to the most subtle forms of brain damage. TMT A and B used in the assessment of survivors of brain tumours by Bordeaux *et al.,* (1988); Copeland *et al.,* (1988) Johnson *et al.,* (1994) and is recommended by (Mulhern *et al.,* 1998).

7.9.4.2. Digit Span

Digit span consists of the raw scores of Digits Forward and Digits Backward and the scale score based on the combined total of Digits Forward and Backward. In Digits Forward the examiner reads a series of digits at one per second and then asks the subject to repeat them. If the subject answers correctly on one of two consecutive trials of the same length, the examiner proceeds to the next series which is one digit longer, up to a maximum of nine digits. For Digits Backwards a similar procedure is used except that the subject must repeat the digits in reverse order up to a maximum length of eight digits. Digit Span is a measure of immediate auditory recall for numbers for which facility with numbers, good attention and freedom from distractibility are required. Performance on the test may be affected by anxiety or fatigue. Digit repetition is considered to be a test of freedom from distractibility in the SSAIS-R and ISX (Van Eeden and Visser, 1992; Landman in Van Eeden *et al.,* 1994). Obtaining adequate control over the ability to sustain and shift attention appears to develop by the age of four years (Butler,1998; Griffiths,1984). Digit

span as a test of attention in children with brain tumours is used by Chapman *et al.,* (1995) and Moore, Ater and Copeland (1992).

7.9.5. VISUAL PERCEPTUAL INFORMATION PROCESSING

THE DEVELOPMENTAL TEST OF VISUAL MOTOR INTEGRATION (VMI or Beery, 1989).

First published in 1967, the VMI is a well researched and internationally accepted test. The 1989 edition was used in the study and administered to both children and adults. The 1989 norms which are based on the 1981 normative sample were found to be virtually identical with the original 1964 sample (Beery, 1989). The revised scoring allows for finer discrimination between the performance of subjects especially at the older age levels (Beery, 1989). Mean scores, standard scores and percentile scores are given for ages three to 18 years. Interrater reliability for the original form is reported from 0.58 to 0.99 (Crosden, 1985 in Spreen and Strauss, 1991).

In the context of a neuropsychological battery for survivors of brain tumours and ALL, the VMI proved useful in America (Brookshire *et al.,* 1990; Moore, Ater *et al.,* 1992; Moore Copeland *et al.,* 1992; Mulhern *et al.,* 1998; Packer *et al.,* 1989; Packer *et al.,* 1988) as well as in South Africa (Roux, 1987). VMI is recommended by Mulhern *et al.,* (1998).
Given the cognitive limitations of the adults in the sample it was decided to use tests which have been shown to be reliable on children. According to Spreen and Strauss (1998) for practical purposes the norms for thirteen and fourteen year olds can be used for older age groups.

7.9.6. Test of Visual Perceptual Skills (non-motor) (TVPS) (1988)

The TVPS was devised by Morrison Gardner (1982) and distributed by the Health Publishing Company in affiliation with the Children's Hospital of San Francisco USA. The 1988 edition is used in interpreting the scores.

A non-motor, short, test, based on a choice between four or five items, was included in the battery to clarify the visual perceptual difficulty. The test has seven scales of visual perceptual skills of which three are used in the study: Visual Discrimination, Visual Memory and Visual Spatial Relationships. The diagnostic validity was shown by finding significant differences in test scores between a learning handicapped group and a matched control group and by establishing the subtest intercorrelations.

Menken, Cermak and Fisher (1987) show that the TVPS is a valuable tool in assessing visual perceptual functioning in children with cerebral palsy. Given the cognitive limitations of the adults in the sample it was decided to use tests which have been shown to be reliable on children. Although the TVPS is designed for children and adolescents Su, Chien, Cheng and Lin (1995) have shown that it can be used on adults.

7.9.7. Memory and Learning

7.9.7.1. Incidental Recall

CODING.

Kaplan, Fein *et al.,* (1991) in Lezak (1995) use Coding both as a measure of incidental recall and a standardized score on the relevant IQ Test. The norms of Spreen and Strauss (1991) were used for children from age 8 years to 12 years. The test requires the subject copy symbols for the numbers one to nine. The examiner notes how long the child takes to complete the test and also records how much of the test the person managed to finish in 90 or 120 seconds, depending on the age of the subject. The examiner then folds the test sheet so that only the unmarked row of digits are shown and the subject is asked to fill in from memory as many of the symbols as can be recalled. A recall of six of the nine symbols is the low range of normal adult recall (Lezak, 1995).

For children the coding is done in standard fashion and on completing the task the child is provided with another sheet of paper containing the numbers one to nine and asked to fill in the associated symbols. One point is awarded for each accurately drawn symbol, while a half a point is given for any accurately drawn but incorrectly associated symbol. Visual perceptual difficulties rather than memory could confound the incidental recall score.

7.9.7.2 Verbal Memory – Immediate Recall (SSAIS-R, scale score)

The story is read slowly to the subject and the examiner writes down verbatim the child's response. Scoring is according to the protocol.

7.9.7.3 Wechsler Memory Scale –REVISED (WMS-R, 1987)

This is an update of the WMS (1945). The revised version is considered an improvement over the original version (Franzen , 1989; Loring, 1989; Powell, 1988 in Elwood, 1991) especially with the addition of the delayed recall data (Loring, Papanicolaou, 1987 in Rourke, Costa, Cicchetti *et al.,* 1991). Wechsler (1987) reports that inter-scorer reliability coefficients for Logical Memory and Visual Reproduction as .99 and .97 respectively. He

also shows the mean reliability coefficients for Logical Memory 1 = .71; 11 =.75 and Visual Reproduction 1 = .71; 11 = .69.

7.9.7.4. Logical Memory (WMS-R, 1987)

The passages from the WMS-R story were developed for the American population. The passages which have been used in the Department of Neurosurgery, Groote Schuur Hospital, over the past decade are a slightly modified form of the American version. They are available in English and Afrikaans and have the same number of items as the WMS-R story. Words in the original text have been changed where necessary to make the story more suited to South African culture:

Story A: Anna Botha instead of Anna Thompson; Bellville instead of Boston; Rands instead of dollars

Story B: National road instead of highway; Hex River Valley instead of Mississippi Delta; Laingsburg instead of Nashville.

All instructions were given as stated in the manual: The stories were read slowly to the subject and the responses written down verbatim. Scoring was done according to the manual and a Percentile score obtained for immediate and delayed recall.

WMS and WMS-R Logical and Visual Tests were used to assess brain tumour patients by Chapman *et al.,* (1995); Johnson *et al.,* (1994) and are recommended as part of a battery (Mulhern *et al.,* (1998).

7.9.7.5. Visual Memory (WMS-R, 1987; TVPS, 1988).

WMS-R, VISUAL MEMORY 1 and 11.

Administered and scored according to the instructions in the manual. Percentile scores for immediate and delayed recall were obtained for the adults. Mulhern *et al.,* (1998) recommend a visual memory test as part of the battery.

The TVPS Gardner, visual memory subtest (non-motor), a brief screening test was included to supplement the other visual perceptual functions and to determine, if possible, the extent of the visual memory difficulty and the contribution, if any, of the visual motor problem (see visual perceptual information). The Percentile scores were used.

7.9.8. Learning

7.9.8.1. Auditory Verbal Learning Test (AVLT)

The norms of Bishop, Knights and Stoddart, (1990) were used for children and those of Wiens, McMinn and Crossen, (1988) for the adults. According to Spreen and Strauss (1991) the AVLT was devised by Swiss psychologist Andre Rey (1964) and adapted by Taylor (1959) and Lezak (1983) for English speaking subjects. The test is a widely used test of verbal memory and new learning in both children and adults. It consists of a list of 15 words (List A) which is read to the subject at a rate of one word per second. The subject is then asked to recall as many of the words as possible, in any order and this is repeated for four additional trials. The order of the presentation of the words remains fixed and instructions are repeated before each trial to minimize forgetting. On completion of trial 5, an interference list of 15 words (List B) is presented and recalled, followed by a recall of the original list (trial 6). After 20 to 30 minutes' delay period, filled with other activities, the subject is asked to recall the items from List A again. The examiner notes the order of the words recalled, repetition of words, words that are not on the list (confabulations) or intrusions from other sources (such as, words from List B).

Examination of the first five trials indicates the quality of the learning curve. Proactive interference can be assessed by comparing recall on Trial 1 (List A) with recall on the distraction trial (List B). Retroactive interference can then be assessed by comparing the number of words recalled on Trials 5 and 7 (delayed recall).

7.9.8.2. Recognition Test – AVLT

On completion of the delay recall trial (T 7), the recognition trial is administered. This task requires the subject to identify as many words as possible, from an array of 50 words derived from List A & B as well as words that are semantically associated with or phonetically similar to words on these Lists. If the subject can read, the subject is asked to read the list and to circle the correct words. If the subject is unable to read, or has difficulty in doing so, the examiner should read the list to the child.

The AVLT has modest test-retest reliability with a correlation of about .55 (Snow *et al.,* 1988, in Spreen and Strauss, 1991). The AVLT is sensitive to laterality of brain damage and to verbal memory deficits in a variety of patient groups (Bigler, Rosa, Schultz *et al.,* 1989; Lezak, 1983; Miceli, Caltagirona, Gainotti *et al.,* 1981; Mungas, 1983; Rosenberg, Ryan and Prifiteria 1984 in Spreen and Strauss, 1991).

7.9.9. Emotional and Behavioural Functions

A short screening measurement to identify children with problem behaviours was needed. Checklists represent an efficient means of sampling a wide range of behaviours that may be present in a child or adolescent. Various tests used in an oncology setting were considered but discarded because they were too long:

7.9.9.1. Walker Problem Behaviour Identification Checklist (WPBIC, 1989)

The 1983 version of the Walker Problem Behaviour Identification Checklist is a revision of the 1970 edition published (1989) and distributed by Western Psychological Services, USA. The checklist fulfils the requirements of Mulhern *et al.*, (1998) for "practice option" and includes 50 items which measure problem behaviours in five areas:

ACTING OUT; WITHDRAWAL; DISTRACTIBILITY; DISTURBED PEER RELATIONS and IMMATURITY. The domains, at face value, seem to be appropriate for children with cancer. In addition to scores for each of the domains, a Total Score is derived to provide a measure of overall problem behaviour functioning.

Although the checklist was designed to be completed by teachers to assess a pupil's classroom behaviour, research has shown that it is useful as a parent's rating device (Mash and Mercer, 1979 in Walker, 1989). The checklist was completed by the parents in the presence of the examiner In this way the examiner was able to overcome any difficulties that the parents may have had with it, and to verify that the behaviours did indeed qualify for inclusion on the list.

Each item is scored as either present or absent and carries a score weight that represents a handicapping influence on the child's adjustment. The scored items are summed up for each domain and a total score calculated. The scores are then converted to a T Score for interpretation. According to the manual, T Scores of 60 or higher on any of the five scales suggest the need for referral for further evaluation and/ or testing.

The 50 selected item behaviours were selected from operational descriptions of behaviours that concerned teachers. The normative sample comprised 1840 children from kindergarten, primary and intermediate school as well as from a school for handicapped children. According to the manual, the item validity indices on the 50 items varied from .03 to .67 indicating that the items discriminate between subjects in the upper and lower 27% of the sample in terms of checklist score. Intercorrelation coefficients among the 50 items ranged from .00 to .83, showing that the items measured separate functions of the same behaviour domain.

7.9.10. Health Related Quality of Life

THE MULTIATTRIBUTE HEALTH STATUS CLASSIFICATION (MHSC)

Feeny *et al.,* in (1992) developed a Multiattribute Health Status Classification for evaluating the functional capacity of survivors of cancer treatment (see Appendix D). The list of attributes has been well researched (Cadman, Goldsmith, Torrence *et al.,* 1986; Cadman and Goldsmith, 1986; Rosenbaum *et al.,* 1990, Feeny *et al.,* 1993) and includes:

PHYSICAL FUNCTION AND MOBILITY
COGNITION
SENSATION (hearing speech and vision)
PAIN
SELF CARE
EMOTION

The ability to function is described by levels that vary from poor to good or normal. The MHSC was filled in by the adult patients (n-13) if they were clinically cognitively intact or otherwise by the parent / care giver (n=38) but the fertility domain omitted as it did not apply to many of the subjects.

The system is an extension of a system developed by Torrance to evaluate outcomes of low birth weight infants (Boyle *et al.,*. 1983, Boyle and Torrence, 1984, Torrence *et al.,* 1982 in Feeny *et al.,* 1993) and by Cadman and colleagues to assess health status in handicapped children (Cadman *et al.,* 1986; Cadman and Goldsmith, 1986).

Feeny *et al.,* (1992) conducted an initial survey using the MHSC on children with ALL, Wilm's tumour and neuroblastoma. A second survey was carried out on children with brain tumours on active treatment and compared with the children in the first survey. The brain tumour children were found to experience higher degrees of morbidity.

Whitton *et al.,* (1997) explores the health status of adult brain tumour patients using a format devised for children and adolescents and showing the overall burden of morbidity to be 80%. The authors have revised the scale as the Health Utilities Index Mark 2 and Mark 3 (HUI2 & HUI3), broadened the Sensation Attribute into two separate attributes; Vision and Hearing, and added another Attribute, Speech. The revised format was not available at the outset of this study, but it appears to have remedied the minor shortfalls in administration of the scale. According to the criteria of Mulhern *et al.,* (1998) the test fulfils the criteria for "practice guidelines" (see Appendix C).

7.10. PROCEDURE

7.10.1. Test Interval

At the time of testing, none of the children were on active treatment regimes of surgery, radiotherapy or chemotherapy and none of the sample had suffered a recurrence of the brain tumour in the years between the treatment and the current neuropsychological assessment. Within the sample four children were tested at < 1 year since Treatment (Group 2 = 2 cases; Group 3 = 2 cases).

7.10.2 Test Conditions

Individual appointments were made for each subject and the assessments were carried out by the clinical psychologists of the Neurosurgery Department in a quiet, airy office. Every effort was made to provide a stress-free environment and to overcome difficulties. Attempts were also made to minimize the possible effects of fatigue on test performance by arranging for tests to be administered in the morning. The subjects were allowed short breaks to minimize fatigue.

Many of the children were known to the psychologist and a good relationship with the families existed. Tea and biscuits were provided for those children who had not had an adequate breakfast or who had travelled a long distance. Transport costs were refunded to those who could not afford them. Employers were requested not to deduct wages for time missed. Letters were written to schools, welfare agencies, work places and referrals made to other hospital departments whenever necessary.

The interview with the parent or the subject included:

- An explanation of the purpose of the research study and the signing of the consent form. Parental consent had to be obtained for subjects under the age of 18 years, or those subjects who did not fully comprehend the purpose of the assessment and were in the care of their family or guardian. The Intake Questionnaire was then completed (see Appendix E).

- The WPBIC and MHSC were completed after the administration of the test battery.

The neuropsychological assessment followed the interview and various tests were administered in a flexible order format, designed to put subjects at ease, create a sense of rapport and reduce any anxiety. Some tests, such as the memory tests, may provide more anxiety than others. When testing children, a flexible approach is needed and where necessary, the order of presentation was changed to suit the demands of the individual. Lezak (1995), in a review of research in this area, concluded that the order of test presentation does not have an appreciable effect on test performance. A typical order of test presentation was as follows:

Purdue Pegboard
AVLT
Trail Making Test (adults)
WMS – R, logical & visual memory scales (adults)
Developmental Test of Visual Motor Integration
Sub-Scales of the appropriate IQ Test (SAWAIS; SSAIS-R; ISX; Griffiths; OASIS)
Successive Finger Taps
Balance
Tandem Gait
AVLT delayed recall
WMS – R, Delayed Recall logical & visual memory scales (adults)

Test of Visual Perceptual Skills (non-motor)

The three mother tongue Xhosa-speaking subjects could all speak English. Two of these were attending schools in which Xhosa and English were the language of tuition. In each case the ISX was administered with the help of an interpreter from the Child Guidance Clinic, University of Cape Town, who had been trained specifically to help in the interpretation of tests and test administration. The third Xhosa speaking subject was tested in English as he was attending the University of the Western Cape and had completed all his schooling in English.

The time taken for the administration of the neuropsychological assessment was approximately 80 to 120 minutes. From the examiner's perspective the test-taking behaviour was appropriate in all cases and the participants were judged to have given their best performance throughout. On completion of the testing, the parents and subjects were all given feedback appointments to discuss the test results.

7.11. TREATMENT OF RAW DATA

Assistance was obtained for the collection of the data from the hospital records by a trained nursing sister and an undergraduate psychology student who entered the data onto summary sheets. Each subject had a research folder with photocopies of relevant medical information such as operation details and treatment progress reports in order to check information. Following the collection of the raw data, the tests were scored according to the directions specified by the various test manuals and entered onto a Test Summary Sheet (see Appendix F).

All data were captured on a computer spreadsheet using Excel Programme from MicroSoft Office 1997, and this information was checked against the raw data with the help of an undergraduate student. A variety of statistical analyses were computed:

- The differences between the treatment groups were analysed by using one way ANOVA for parametric data and frequency tables for non-parametric data

- The relationships between the variables were explored by means of Pearson's Product Moment Correlation Coefficient

- Multiple regression analysis were carried out to predict which variables predicted outcome in terms of neuropsychological functioning and quality of life

- Taking the test variables which had differed significantly between the treatment groups, plus prorated FSIQ scores, the following ad hoc analyses were conducted:

- Age-at-Diagnosis: All the subjects were categorically grouped according to whether they were < 4 years; 4-6 years; > 7 years- at-Diagnosis. The ANOVA was done to determine whether there were significant differences in the test results according to the Age–at-Diagnosis.

- Years-since-Treatment: All the subjects were categorically grouped according to <4 years; 4-6 years; 7-10 years; 10+ years - since Treatment. The ANOVA was done to determine whether there were significant differences in the test results according to the variable Years- since- Treatment.

- It was decided to repeat this analysis on the medulloblastoma group in order to be able to see if the variable age effects detected by Dennis *et al.*, (1996) could be replicated on Age-at-Diagnosis and Years-since-Treatment. Multiple regression analysis done on the predictors of Age –at- Diagnosis and Years-since-Treatment failed to show the

predicted change in IQ score. When these results were not significant, those subjects over 18 years old were excluded (Dennis *et al.,*. 1996 only had subjects < 18 years) and the analyses repeated.

- The analysis was then repeated for the astrocytoma subjects, all of whom were younger than 18 years of age, and had been treated by surgery only.

- In order to explore if the type of tumour or the treatment was influencing the cognitive outcome as measured by prorated FSIQ scores, further statistical analysis was done on the medulloblastoma subjects. Medulloblastoma subjects were chosen as there were sufficient numbers to carry out the analysis (n=30). A t-test was applied to determine if there were significant differences between the medulloblastoma subjects treated by means of surgery and radiotherapy (Group 4) and those treated by means of surgery, radiotherapy and chemotherapy (Group 3). Thereafter the ANOVA was computed to assess the extent to which each of the categorical variables, SES and Treatment Group, discriminate between the medulloblastoma cases assessed on prorated FSIQ scores. A further ANOVA was computed to investigate the effect of SES on the prorated FSIQ scores.

- Principal Component Analyses:

- Cognitive variables that had proved sensitive to differences between the groups or major variables like prorated FSIQ were included in a principal component analysis in order to reduce the number of outcome variables to one or two principal components.

- The independent predictors were then entered into a stepwise regression analysis to build a model for predicting the outcome components. Some of the independent variables are categorical (e.g.

shunt revision/no shunt revision), tumour type divided into medulloblastoma/astrocytoma, some ordinal (e.g. treatment groups, SES) and some continuous (e.g. Age-at-Diagnosis, Years-since-Treatment, Age-at-Testing).

- The effect of Type 1 error per comparison was controlled by the selection of the significance level, which means that the level of the risk is controlled. In this way the analysis will yield results which lead to an incorrect rejection of the null hypothesis only a certain proportion of the time (for example, p=.05). In an attempt to control the likelihood of Type 1 errors, the Fisher's least significance difference (LSD) was calculated when the F for the ANOVA was significant The Fisher's LSD test guarantees that the probability of making at least one Type 1 error will not exceed .05 (Howell, 1995). The Bonferroni test is a multiple comparison procedure in which the familywise error rate is divided by the number of comparisons (Howell, 1995). As the present study involved many comparisons this technique was rejected in favour of the Fisher LSD test. Thus every effort was made to minimize the probability of a Type 1 error.

- Type 11 error, the probability of not finding a difference between the groups, that is there, may also occur. Attempts to minimize the probability are difficult as the sample size is small.

CHAPTER 8

NEUROPSYCHOLOGICAL TEST RESULTS

8.1. INTELLIGENCE

Table 8-1 *Summary table of Means on prorated IQ Scores (Griffiths, SSAIS-R, ISX, SAWAIS and OSAIS)*

	GRP 1 n=12	GRP 2 n=20	GRP 3 n=19	ALL GRPS	ANOVA (df = 2,48) F	p-value
FIQ						
X	78.50	80.95	69.89	76.25	1.63	.205
SD	16.74	21 53	19.36	19.96		
Range	51-110	40-118	40-105	40-118		
VIQ						
X	78.33	84.00	72.81	78.27	1.67	.197
SD	15.60	22.48	19.86	20 37		
Range	58-108	40-135	40-107	40-135		
PIQ						
X	81.42	79.50	69.05	76.06	1.65	.200
SD	20.83	22.61	20.29	21.64		
Range	46-119	40-116	40-105	40-119		

In Table 8-1 and Figure 8-1 the Analysis of Variance indicates no statistically significant differences in performance between the treatment groups in prorated FIQ, VIQ or PIQ. The difference between the VIQ and PIQ for the total sample is also not statistically significant This was established by determining a 95% confidence interval -on the difference which was (-1.54, 5 97). The trend as shown in Table 8-1 and Figure8-1 is for Group 3 to have the lower mean scores in prorated FSIQ, VIQ and PIQ. The mean prorated FSIQ, VIQ and PIQ scale scores of age appropriate different IQ test scores however, appear in the Appendix G.

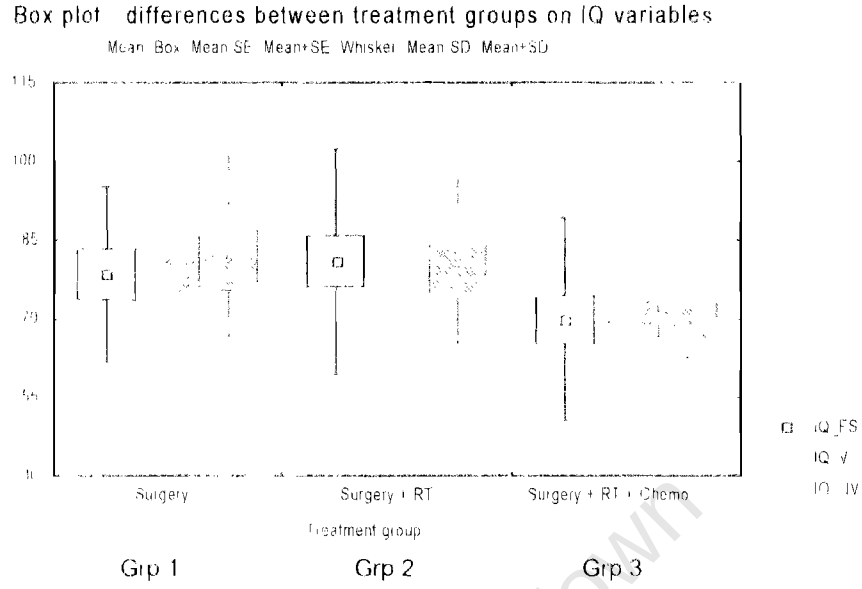


Figure 8-1 *Differences between Treatment Groups on IQ Scores*

Table 8-2 *Summary of Mean Verbal Subtest Scale Scores (SAWAIS, SSAIS-R, ISX)*

	GROUP 1	GROUP 2	GROUP 3	
		COMPREHENSION		ANOVA (df = 2,38)
	n=10	n=16	n=15	F / p-value
X	7 20	8.81	6 47	1.91 / 162
SD	1.69	3.51	4.07	
		SIMILARITIES		
X	6 90	7 75	5.93	0 85 / .434
SD	5.11	3.42	3.49	
		DIGIT REPETITION		ANOVA (df = 2,41)
	n=10	n=17	n=17	F / p-value
X	8.40	8.00	5 17	3 77 / .031
SD	4 09	3.29	3.36	

significant at p< 05

There is no statistically significant difference in performance between the treatment groups in the Comprehension or Similarities subtests. However,

a non-significant trend is shown for Group 3 to have a poorer performance than the other groups in both these subtests.

However, there is a statistically significant difference in performance in Digit Repetition, where the mean scale score trend indicates that Group 3 has the most impaired performance. This is discussed in Section 2.

Table 8-3 *Summary of Mean Performance Subtest Scale Scores (SAWAIS, SSAIS-R, ISX)*

	GROUP 1	GROUP 2	GROUP 3		
	BLOCK DESIGN			ANOVA (df = 2,38)	
	n=10	n=17	n=14	F	p-value
X **SD**	8.70 2.67	7.76 2.28	5.21 3.48	4.47	.017
	CODING			ANOVA (df = 2,38)	
	n=10	n=15	n=12	F	p-value
X **SD**	7.60 2.99	7.53 3.54	3.67 2.77	6.13	.005

significant at p<.01

The summary table indicates a statistically significant difference in functioning between the treatment groups in Block Design. A post- hoc analysis using the Fisher Least Significant Difference (LSD) clarifies that the significant difference is between Groups 1 and 3 (p< .008) and Groups 2 and 3 (p<.025). Group 3, the medulloblastoma tumour subjects, treated by means of surgery, RT and chemotherapy, is the most impaired.

There is also a statistically significant difference in performance in Coding. Fisher LSD shows that the difference is between Groups 1 and 3 (p<.006) and Groups 2 and 3 (p <.003). Group 3 is thus significantly impaired relative to the others in both Block Design and Coding which are both timed tests of Visual Motor Integration.

8.2. ATTENTION

Table 8-4

Summary of Mean Scale Score on Digit Repetition and Mean Percentile Score on Trail Making Test A and Test B.

	GROUP 1	GROUP 2	GROUP 3	ALL GROUPS
		Digits		
	n=10	n=17	n=17	n=44
X	8.40	8.00	5.17	7.00
SD	4.09	3.29	3.36	3.73
		TMT A		
	n=3	n=10	n=5	n=18
X	3.67	19.60	9.00	14.00
SD	5.51	27.79	17.46	22.99
		TMT B		
	n=3	n=10	n=5	n=18
X	39.00	23.78	20.50	25.62
SD	0.00	22.39	28.99	21.00

significant at p<.05

In table 8-4 the ANOVA shows a statistically difference in performance on Digit Repetition (F=3.77; df=2.41; p<.031). Group 3 has the lowest mean scale score.

Digit Repetition is normally reported as digits forwards and digits backwards, in this instance it was difficult to do that kind of analysis as the age range of the sample would have confounded the results. Results were therefore computed on the scale scores. However, differences in raw scores between Digits Forwards and Digits Backwards were calculated to establish if the mean treatment group differences in scores exceeded three digits which would have suggested a difficulty in mental flexibility (mean differences=1.8; 1.6; 1.6). No difference between the groups was apparent.

The numbers in TMT A & TMT B are insufficient for statistical analysis. The mean percentile scores indicate that the subjects have achieved better in Part B than Part A. This suggests that the difficulty could be one of motor slowing and concomitant visual perceptual difficulties, rather than double mental tracking.

8.3. VISUAL PERCEPTUAL INFORMATION PROCESSING

Table 8-5 *Summary of Mean Percentile Scores on Non-Motor Visual Discrimination and Visual Spatial Relations (TVPS) and Visual Motor Integration (Beery)*

	GROUP 1	GROUP 2	GROUP 3		
	Visual Discrimination – TVPS			ANOVA (df = 2,40)	
	n=11	n=16	n=16	F	p-value
X	76.27	53.44	39.25	2.80	.072
SD	32.92	45.53	38.40		
	Visual Spatial Relations – TVPS				
	n=11	n=16	n=16		
X	11.00	12.69	8.69	2.29	.114
SD	4.34	4.76	6.23		
	Visual Motor Integration-Beery			ANOVA (df = 2,42)	
	n=11	n=16	n=18	F	p-value
X	41.00	19.75	9.39	6.48	.003
SD	31.76	23.38	15.19		

significant at p<.01

In Table 8-5 the Analysis of Variance shows that there is a statistically significant difference in performance between the treatment groups in Visual Motor Integration (Beery). A post hoc analysis using the Fisher (LSD) shows that the significant difference in performance is between Groups 1 and 2 ($p < .023$) and Groups 1 and 3 ($p < .0008$), the functioning of Group 3 being the most impaired.

The Visual Discrimination and Visual Spatial Relations tests are "motor free" tests which have not elicited a significant difference in performance between the treatment groups. However, a downward trend is shown in the mean percentile scores in Visual Discrimination according to the addition of treatment whereas the scores in Visual Spatial Relations are within the impaired range for all the treatment groups

The Analysis of Variance between the two non-motor tests, Visual Discrimination Test and the Visual Spatial Relations Test, shows that there is a significant difference in performance between the results of the two tests. ($df=2,40$; $F=2.512$, $p < .050$).

The overall impaired performance of the subjects in the Visual Spatial Relations Test is significantly worse than the overall performance on the Visual Discrimination Test ($t = 6.5$; $df=42$; $p < .0001$).

In summary in the domain of Visual Perceptual Information Processing, the results of the above tests, plus the results obtained on the Block Design and Coding tests, indicate that the subjects in Group 3 are significantly impaired on both the motor-free tests and the motor tests of Visual Perceptual Information processing. In terms of Visual Spatial Relations (non-motor) the performance of all the subjects is within the impaired range.

8.4. MEMORY

Table 8-6 *Summary Table of Mean Scale Scores on Story Memory, (SSAIS-R) and Mean Percentile Scores on - Logical Memory (WMS-R)*

	GROUP 1	GROUP 2	GROUP 3
	Story Immediate Recall – SSAIS-R		
	n=8	n=6	n=8
X	11.50	11.00	10.50
SD	6.16	8.17	6.54
	Story Immediate Recall – WMS-R		
	n=2	n=10	n=4
X	30.50	39.10	8.25
SD	20.15	31.18	10.58
	Story Delayed Recall – WMS-R		
X	33.50	41.40	10.25
SD	19.09	33.07	8.66

In the above table, descriptive statistics are presented as the number of subjects in some groups are insufficient for statistical analysis.

School-going children from the ages of 7 years to 17 years 11 months participated in the SSAIS-R story memory test. The overall trend of the mean scale scores of the three treatment groups indicates that they are all functioning within the average range in immediate recall of a story.

Subjects 18 years and older completed the WMS-R test. The mean percentile score of the Story (logical) Memory on both Immediate and Delayed Recall shows that both Group 1 and Group 2 are functioning in the 30.5 – 41.4 percentile range whereas Group 3 are in the impaired range on both Immediate and Delayed recall. The small numbers in each group and the large variation in standard deviation scores preclude further analysis.

The Age-of-Testing for those who did the WMS-R is from 18 years to 42 years, representing an older age group than the children who were tested on the SSAIS-R Story Memory. Although it is difficult to compare the results of two different tests, the mean percentile scores of the Story Memory WMS-R show that the group is functioning from the low average to impaired range whereas the Mean Scale scores of the SSAIS-R are within the average range. It is possible that Age-at-Testing and Years-since-Treatment may have influenced or played some part in these results.

Table 8-7 *Mean Percentile Scores on Visual Memory (TVPS non-motor WMS-R,)*

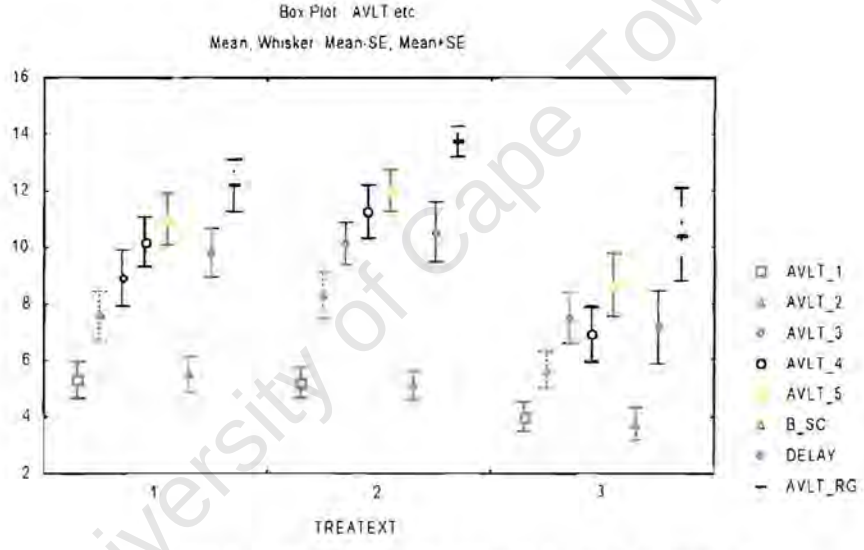
	GROUP 1	GROUP 2	GROUP 3
	Visual Immediate Recall – WMS-R		
	n=2	n=10	n=4
X	36.50	61.80	35.75
SD	34.65	33.26	42.87
	Visual Delayed Recall – WMS-R		
X	46.00	50.50	21.25
SD	33.94	39.25	35.22
	Visual Immediate Recall – TVPS non-motor		
	n=11	n=16	n=16
X	50.91	59.94	26.04
SD	26.44	35.14	33.82

significant at p<.05; significant at p<.01

On the TVPS–non-motor test of Immediate Visual Recall, there are statistically significant differences in functioning between the treatment groups according to ANOVA calculation ($F=5.91$; $df=2.40$; $p<0.005$). Post-hoc analysis using the Fisher (LSD) shows that the significant difference in functioning between Groups 2 and 3 is just short of statistical significance ($p < .058$) but that there is a statistically significant difference between Groups 2 and 3 ($p < .006$). Group 3 has the most impaired level of functioning. As most of subjects over the age of four years were able to participate in the test, the sample is larger than the number of subjects completing the WMS-R. The robustness of the statistical results are thus enhanced by the larger number of participants.

On the WMS-R Visual Memory the small number of subjects restrict the analysis. A trend is shown for Group 2 to perform better both in Immediate and Delayed Visual Recall and for Group 3 to perform the worst on Delayed Visual Recall. Interestingly, Group 1 have improved their percentile scores from Immediate to Delayed recall, suggesting a minimum or no loss of information, whereas Group 2 and 3 have lost information.

8.5. LEARNING



AVLT 1 = TRIAL 1 AVLT 2 = TRIAL 2 AVLT 3 = TRIAL 3
AVLT 4 = TRIAL 4 AVLT 5 = TRIAL 5 B_SC = INTERFERENCE
DELAY = DELAY AVLT_RG = RECOGNITION

Figure 8-2 *AVLT Learning Curve*

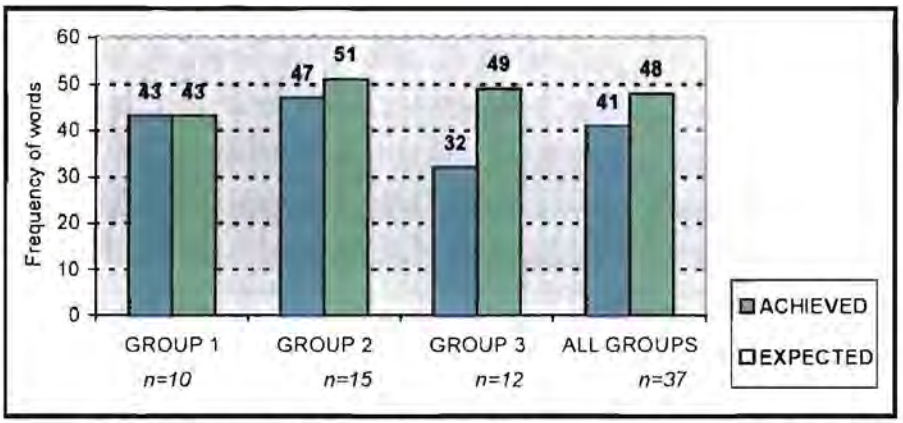


Figure 8-3 *Histogram of Total Words Achieved and Expected on AVLT*

In the Figures 8-2 and 8-3 the trend of the Learning Curve indicates that all the groups have the ability to learn a list of words after repeated rehearsal.

However, Group 3 is slow to start (Trial 1), and appear to have difficulty in sustaining their attention (Trials 3 and 4), although they regain their momentum (Trial 5). After an interference task (B), Group 3 have difficulty in shifting their response from one task to another. The differences between the groups are significant for Trial 4 ($F=5.92$ $p < 006$) and Trial 5 ($F=3.65$; $p < .036$).

There is a statistically significant difference between the groups in the Total Number of Words Recalled ($df=2,34$; $F=4.14$; $p < 05$). A post hoc analysis, (LSD <.007) shows that the significant difference is between Groups 2 and 3.

The ANOVA ($df=2, 33$; $F = 2.60$; $p > .089$) indicates that there are no statistically significant differences between the groups in terms of their performance on the Recognition score.

Table 8-8 *Supplementary Indices of the Auditory Verbal Learning Test*

	GROUP 1 n=10	GROUP 2 n=15	GROUP 3 n=12
Learning over trials (cumulative T1-T5 minus 5 x T1)	16.5	21.25	12.75
% retention (T5-T6)	69.6%	75.1%	52.5%
Long term % retention (T5-T7)	69.3%	75.1%	52.8%
Learning Index (highest score T1-T5 minus T1)	5.7	6.8	4.67
AVLT TRIAL 1 and DIGITS FORWARD			
Trial 1 AVLT	5.30	5.20	4.00
Digits Forward X Score	4.67	5	4.26

The Supplementary Indices clarify the quality of the subjects' ability to learn. Qualitatively, Group 2 appear to have marginally better scores in learning over trials and in ability to retain both long-term and short-term information. Group 3, on the other hand have the poorer scores. The scores are almost identical for Short Term Retention and Long Term Retention.

The Number of Words Recalled on Trial 1 of AVLT are similar to the Number of Digits Forwards Recalled for each group (5,5,4 versus 4,5,4).

8.6. MOTOR FUNCTIONS

Table 8-9 *Purdue Pegboard: Summary of Mean Percentile Scores*

	GROUP 1 n=11	GROUP 2 N=18	GROUP 3 n=17	ANOVA (df = 2,43) F	p-value
Preferred Hand					
X	26.33	35.00	14.12	3.76	.031
SD	20.10	29.15	14.16		
Non-Preferred Hand					
X	20.19	35.00	14.12	4.67	.014
SD	18.14	23.84	8.70		
Both Hands					
X	40.00	29.44	14.12	4.39	.018
SD	33.76	23.88	11.76		

significant at $p < .05$; significant at $p < .01$

The summary table shows that there is a statistically significant difference between the treatment groups in performance on all three measures of the Purdue Pegboard.

Post-hoc analysis using the Fisher (LSD) on all the parameters indicates that Group 2 is significantly better than Group 3 on both the Preferred Hand Functioning ($p < .009$); and the in Non-Preferred Hand Functioning ($p < .006$); and that in Both Hand Functioning Group 2 is significantly better than Group 3 ($p < .058$), and Group 1 is significantly better than Group 3 ($p < .006$).

There are no statistically significant differences between Group 1 and 2.

The trend of the mean percentile scores of the entire group, with the exception of the Surgery group's performance when using Both Hands, indicate that the sample is functioning within the borderline to impaired range in Preferred, Non Preferred and Both Hands. The larger standard deviation score of the Surgery group highlights that the scores of the group are more widely dispersed than the other scores. In Group 3, the

medulloblastoma subjects who had surgery, RT and chemotherapy, all had scores within the impaired range.

8.6.1 Successive Finger Taps

Table 8-10 *Mean time taken (in seconds) to perform Successive Finger Taps*

	GROUP 1 n=11	GROUP 2 n=17	GROUP 3 n=14	ALL GROUPS n=42
PREFERRED HAND				
Mean				
Observed	10.27	8.41	10.93	9.74
Expected	8.82	7.41	7.71	7.88
Difference	1.45	1	3.22	1.86
NON-PREFERRED HAND				
Mean				
Observed	10.10	8.71	11.43	9.98
Expected	9.60	7.74	8.00	8.17
Difference	0.50	0.97	3.43	1.81

The summary table of mean differences in seconds between the observed and expected scores to execute Successive Finger Taps indicates that Group 3 is slower than the other groups in the performance of the task using the Preferred Hand and the Non- Preferred Hand. The significant difference was established at the 95% Confidence Level on the difference in time (seconds) on the Preferred Hand functioning (0.737; 2.976) and Non-Preferred Hand functioning (0.621;2.988). The difference is significant as the interval does not include 0.

8.6.2 Balance and Gait

Table 8-11 *The number of Subjects in each group (expressed as percentage) who could maintain their Balance on the Preferred and Non-Preferred Leg*

	GROUP 1 n=11	GROUP 2 n=19	GROUP 3 n=19	ALL GROUPS n=49
PREFERRED LEG				
%	(4) 36%	(16) 84%	(4) 21%	(24) 49%
NON-PREFERRED LEG				
%	(7) 64%	(13) 68%	(3) 16%	(23) 47%

Adequate norms are not available for this test but the expected age appropriate scores for boys and girls of Denckla (1973, 1974) were used. The trend in the table shows that a large number of children in Group 3 had difficulty balancing on either leg. The statistically significance of differences were established by determining the 95% confidence level on the differences which were (-17.76; -6.60) preferred leg and (-19.07; -8.67) non-preferred leg.

Table 8-12 *Ataxic Gait 2-Way Summary Table: Observed Frequencies*

	GROUP 1 n=11	GROUP 2 n=19	GROUP 3 n=19	TOTALS n=49
Ataxic Gait	(4) 36%	(9) 47%	(12) 63%	(25) 51%

The summary table shows a trend for an increasing proportion of subjects from Group 1 to Group 3 to have ataxic gait but the difference did not reach statistical significance (Pearson Chi-Square, 2.167; df=2; p >.338).

8.7. THE EFFECT OF TUMOUR TYPE

Table 8-13 *The Means and Standard Deviations of Tumour Types on Cognitive Variables*

	ASTRO-CYTOMA	EPENDYMOMA	MEDULLO-BLASTOMA	BRAIN STEM GLIOMA
		Prorated FSIQ		
	n=16	**n=4**	**n=30**	**n=1**
X	79.12	68.25	75.90	73.00
SD	21.19	17.63	20.20	0.00
		TVPS- MOTOR VISUAL MEMORY PERCENTILES		
	n=13	**n=3**	**n=26**	**n=1**
X	9.23 P	12.00 P	8.84 P	73.00 P
SD	3.21	4.00	4.66	0.00
		AVLT/RAW SCORES		
	n=11	**n=3**	**n=22**	**n=1**
X	44.18	42.00	39.90	42.00
SD	12.36	14.00	15.87	0.00
		VMI-BEERY PERCENTILES		
	n=13	**n=3**	**n=28**	**n=1**
X	42.53 P	2.33 P	13.21 P	6.00 P
SD	30.05	1.52	18.47	0.00
		PURDUE/BOTH HANDS PERCENTILES		
	n=14	**n=4**	**n=27**	**n=1**
X	37.14 P	27.50 P	21.11 P	10.00 P
SD	31.23	35.00	18.67	0.00

The small numbers in some groups are insufficient for statistical analysis. The prorated FSIQ scores show that the astrocytoma and medulloblastoma groups are both in the borderline range, whereas the ependymoma group, all of whom had the same treatment of Surgery + RT are in the mental retardation range. The small numbers of subjects across the groups as well as the different treatment modalities and possibly the severity of the various tumours are complicating factors in the interpretation of the results.

With the exception of the single case in the brain stem glioma tumour group, the mean percentile scores of all the subjects in the astrocytoma

tumour group, ependymoma tumour group and the medulloblastoma tumour group are within the impaired range on Visual Memory (TVPS) non-motor functioning.

Raw scores between the tumour groups on the AVLT total scores show a downward trend with the medulloblastoma group having the lowest scores but indicating that the survivors are capable of learning a novel list of words with repetition and rehearsal.

On the Visual Motor Integration Test (Beery) the astrocytoma brain tumour mean percentile scores are in the average range whereas the medulloblastoma scores are in the below average range. The astrocytoma tumour group comprises of low grade tumours as well as tumours of higher grades treated by means of surgery only as well as surgery and radiotherapy. The medulloblastoma tumour groups are malignant tumours treated with surgery and radiotherapy or surgery, radiotherapy and chemotherapy. Treatment is thus a potential confound in the interpretation of the results. The scores of the ependymoma tumour group are in the impaired range.

The different treatment variables, small numbers, wide scatter of the scores as well as the retrospective nature of the design are potential confounds in the interpretation of the results. In Chapter 10 the effects of age and time on tumour type are evaluated. Chapter 11 explores the factors that are influencing the outcome of the medullobastoma tumours subjects. Appendix A shows the histology of the various tumours.

8.8. SURGICAL RESECTION AND SELECTED POST TREATMENT COMPLICATIONS

Table 8-14 *The Effects of Surgical Resection and Selected Post Treatment Complications on prorated FSIQ*

SURGERY		SUBTOTAL n=26	TOTAL n=25	ANOVA (df = 1,49)	
				F	p-value
	X	73.38	79.24	1.09	.299
	SD	20.69	19.10		
MUTISM		**MUTE n=6**	**NOT MUTE n=45**	**ANOVA (df = 1,49)**	
				F	p-value
	X	73.83	76.57	1.91	.483
	SD	14.91	20.89		
REPEATED SHUNT REVISION		**SHUNT n=40**	**REPEATED SHUNT n=11**	**ANOVA (df = 1,49)**	
				F	p-value
	X	81.07	58.72	13.53	.0005
	SD	18.02	17.12		
SEIZURES		**SEIZURES n=3**	**NO SEIZURES n=48**	**ANOVA (df = 1,49)**	
				F	p-value
	X	57.33	77.43	2.97	.090
	SD	15.01	19.74		

significance at p <.001

The table shows there are no statistically significant differences in prorated FSIQ scores between the children undergoing subtotal and total tumour resections or between those rendered mute and not mute following surgery. There is a statistically significant difference between those undergoing repeated shunt revisions and those not having a repeated shunt revision. The difference in prorated FSIQ scores between the three patients suffering from seizures and those who do not does not reach statistical significance, possibly due to the small numbers involved.

Table 8-15 *The Height and Weight Mean Percentile Scores*

	GROUP 1	GROUP 2	GROUP 3		
	WEIGHT			ANOVA (df=2,48)	
	n=12	n=20	n=19	F	p-value
X	44.00	36.65	26.26	1.15	.324
SD	35.33	35.00	28.15		
	HEIGHT			ANOVA (df=2,47)	
	n=12	n=19	n=19	F	p-value
X	55.41	39.89	23.42	3.33	.044
SD	35.55	37.35	29.19		

significance at p< .05

Although there is no statistically significant difference in weight between the treatment groups, the table shows a trend for decreasing weight as radiotherapy and chemotherapy are added to the treatment protocols.

There is a statistically significant difference in percentile height between the treatment groups showing that Group 3 have the shorter stature (Fisher's LSD p =.01).

8.9. SOCIO-ECONOMIC STATUS AND EFFECTS ON PRORATED IQ SCORE

A marginally significant correlation between the occupational status of the sample and prorated IQ scores shows that the higher the occupational status the higher the prorated IQ score (see tables 8-16 and 8-17 below)

Table 8-16 *Prorated IQ and Occupational Status in Entire Group*

	FIQ	VIQ	PIQ
Occupation	.288	.285	.276
P	.041	.042	.050

Table 8-17 *Prorated IQ according to Occupational Status Groups in each occupational category*

Occupational Status		FIQ	VIQ	PIQ
Professional & Managerial n=6	Means	80.16	82.16	79.00
	SD	28.24	28.23	27.14
Middle White Collar n=12	Means	93.00	94.91	93.83
	SD	21.31	21.80	23.15
Manual Foreman & Skilled n=17	Means	67.23	69.47	67.23
	SD	13.68	15.00	16.64
Routine Non Manual n=11	Means	73.27	75.18	72.45
	SD	10.36	11.23	13.80
Unskilled Manual n=5	Means	68.60	70.40	67.80
	SD	19.83	19.52	21.42
All Groups n=51	Means	76.54	78.27	76.05
	SD	19.95	20.37	21.63

One way ANOVA on the three prorated IQ measures with Occupational status as the independent variable shows that there are expected significant differences between the occupational categories on FSIQ (df=4;F=4.09; p=.006), VIQ (df=4;F=3.79;p=.009), PIQ (df=4; F=3.66; p=.011). The summary table indicates that Occupational category group 2 (Middle white collar class) is higher than Occupational categories 1(Professional and managerial), 3 (Manual, foreman and skilled), 4 (Routine non manual) and 5 (Unskilled manual). However, as shown in Table 7-4, there are no significant differences between the Treatment Groups according to Occupational Status.

CHAPTER 9

QUALITY OF LIFE

9.1. INTRODUCTION

Quality of Life refers to how well the survivors are functioning in the domains of emotion, behaviour, health, education and occupational status. The WPBIC was administered to all school-going children and the MHSC was given to the entire sample.

9.2. WALKER PROBLEM BEHAVIOUR IDENTIFICATION CHECKLIST

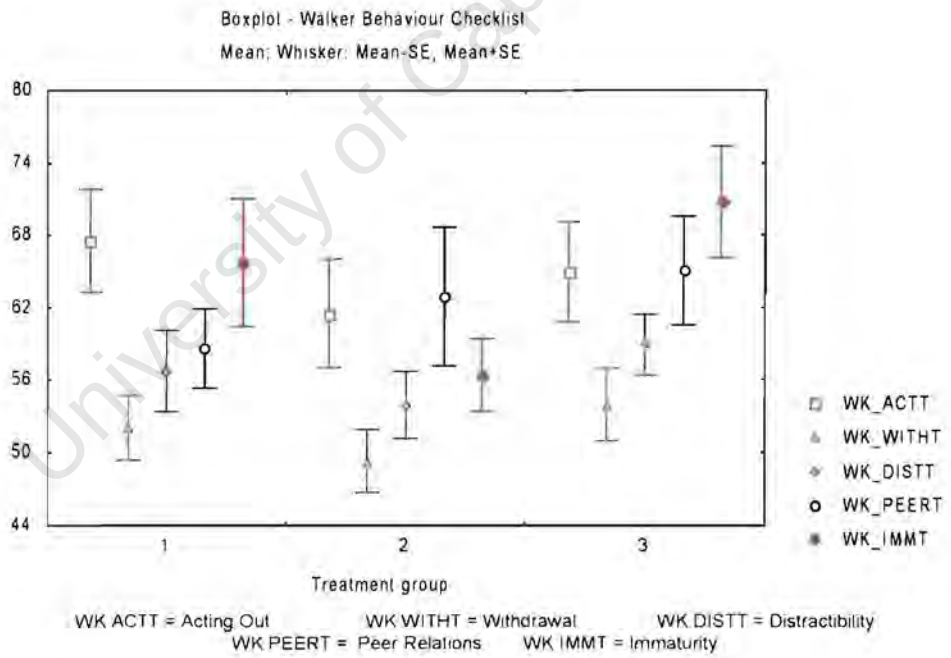


Figure 9-1 *Summary of Mean T Scores on WPBIC*

In the Figures 9-1 and 9-2, the Analysis of Variance shows no significant difference between the treatment groups in: Acting Out (F= 0.46; df=2, 31;

p > .636); Withdrawal (F= 0 .67; df=2, 31; p >.518); Distractibility (F=0.75; df=2.31,p > .480); Disturbed Peer Relations (F= 0.53; df=2, 31; p >.593); Immaturity (F= 2.51; df=2, 31; p > 0 .097) and Total T Score (F= 1 18; df=2, 31, p > 320).

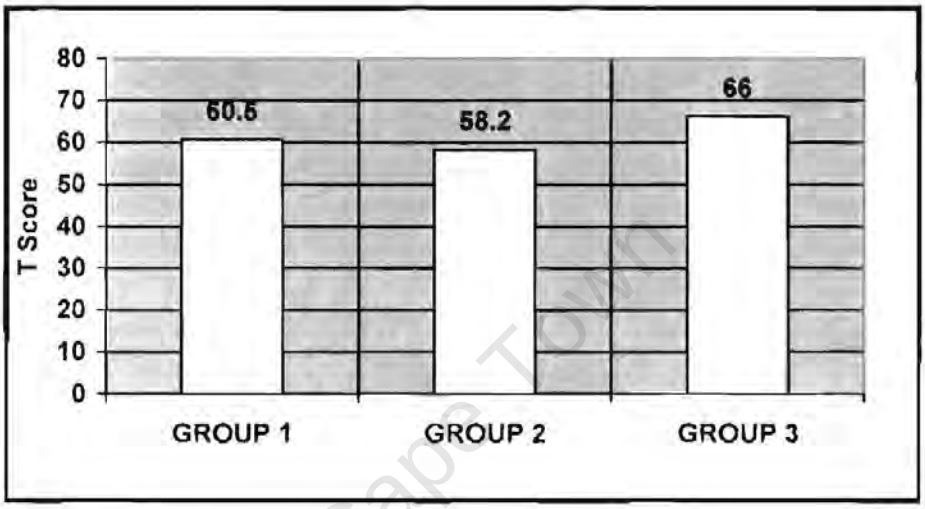


Figure 9-2 *Mean Total T Scores on WPBIC*

A score between T40-T60 is considered to be within the average range: the higher the score the more impaired the functioning. The trend of the total scores indicates that Group 1 and Group 2 are functioning within the upper limits of the average range, whereas Group 3 falls in the below average range in terms of problem behaviour. Figure 9-1 demonstrates the domains of difficulty experienced by each group:

- Acting Out (ACTT) this is a problem behaviour for all the groups
- Immaturity (IMMT): all the children in Group 3, the majority of those in Group 1, but none in Group 2 are immature
- Disturbed Peer Relation (DISTT): more than half the children in Groups 2 and 3 have difficulties with this domain

- Withdrawal and Distractibility (WITHT; DISTT): few children in the treatment groups have difficulties in these areas

9.3. AGE-AT-DIAGNOSIS AND WPBIC

The effects of Age-at-Diagnosis on psychosocial functioning are seldom described. Age-at-Diagnosis and WPBIC total score are not significantly correlated (r=.077; p=.667).

9.4 WPBIC AND NEUROPSYCHOLOGICAL TESTS

An analysis was done to explore the possibility of an association between problem behaviour and cognitive deficits with the neuropsychological tests found to be sensitive to differences between the treatment groups.

Table 9-1 *Correlation on WBPIC and Cognitive Test Results*

	FSIQ n=34	TVPS-VM n=31	AVLT TOTAL n=25	VMI-BEERY n=34	PURDUE BOTH n=31
WPBIC	-.380	-.329	-.212	-.219	-.214
Total	p<.027	p<.071	p>.307	p>.230	p>.248

significant p<.05

The above table shows a statistically significant albeit moderate, negative association between prorated FSIQ and total score on WBPIC, with problems increasing as FSIQ decreases.

9.5. HEALTH RELATED QUALITY OF LIFE

Functional Morbidity (MHSC)

The functional morbidity of the sample, is the sum of the number of attributes scored in each domain of sensation, mobility, emotion, cognition, self care and pain, on MHSC. Attribute level 1 describes normal

developmental functioning for the specific age. Attribute level 5 describes the most impaired level of functioning in each domain. Subjects may endorse different levels of function in the domains.

Table 9-2 *Frequency of Functional Level Endorsed expressed as percentages (MHSC)*

LEVEL OF ATTRIBUTES AFFECTED	NUMBER OF PATIENTS REPORTED (%)
1	18 (36%)
2	9 (18%)
3	11 (21%)
4	8 (15%)
5	5 (10%)
TOTAL	51 (100%)

The above table indicates that 36% of the sample have only endorsed attribute level 1 indicating that they have no functional difficulties. Thus, 64% of the sample have some degree of functional morbidity (percentages have been rounded off for ease of interpretation).

Table 9-3 *Frequencies of Domains of Attributes Affected –MHSC*

Attribute Level	Sen-sation	Mobility	Emotion	Cognition	Self Care	Pain
1	36 (70%)	28 (55%)	23 (45%)	15 (29%)	40 (78%)	45(82%)
2	11 (22%)	18 (35%)	23 (45%)	12 (24%)	8 (16%)	6 (12%)
3	2 (4%)	3 (6%)	5 (10%)	21 (41%)	0	0
4	2 (4%)	1 (2%)	0	3 (6%)	3 (6%)	0
5	-	1 (2%)	0	-	-	-

n=51

This table shows the level of attributed difficulty found in each domain of functioning.

Sensation: Within the sample, 22% of the subjects require some form of equipment such as glasses or a hearing aid to see or hear adequately. Unfortunately, however, the scale does not differentiate between the

various sensations: The hearing and vision of two subjects is limited, in spite of equipment. One late survivor is mute and another blind.

Mobility: Only about one third (35%) of the sample endorsed attribute level 2, which describes limitations in locomotor ability such as gait disturbances and difficulties in balance. The scale does not include upper limb movements or differentiate between left-side or right-side functioning. A small number of subjects (6%) require wheelchairs or some form of mechanical aid while 2% require the assistance of another person as well as mechanical aid. Only one patient endorses the criteria for Attribute level 5 in that he is unable to use his legs or one arm.

Emotion: Almost half the subjects suffer occasional emotional turmoil such as fretfulness, anger, anxiety, depression or night terrors whereas only 10% often complain about these symptoms.

Cognition: This category has the highest level of difficulties as 41% of the survivors require educational assistance and 6% are unable to learn.

Self-Care: A small number of subjects require the assistance from another person in activities in daily living such as eating, bathing, dressing or toilet use.

Pain: A high percentage of patients are free of pain and only 12% report occasional pain which is relieved by non-prescription drugs.

9.6. TREATMENT GROUPS AND MHSC

Table 9-4 *MHSC Treatment Group Functioning*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
Mean Total Score SD	8.50 2.54	9.00 3.76	10.26 2.76	9.35 3.18

The above table indicates that the trend is for the mean total score to increase from Group 1 to Group 3 indicating the presence of one or more health-related difficulties. The Anova shows that the difference between the treatment groups is not statistically significant (F=1.35; df=2; p>.268).

9.7. AGE-AT-DIAGNOSIS AND YEARS-SINCE-TREATMENT

9.7.1 Age-at-Diagnosis

Statistically significant correlations were not found for the group as a whole between Age-at-Diagnosis and MHSC domain scores: Sensation (r=.074; p>.607), Mobility (r=-109; p>.446), Emotion (r=.114; p>.424), Cognition (r=-139; p>.330), Self Care (r=-.219; p>.123), Pain (r=.148; p>.299) or the total Score (r=-.067;p>.639).

As more than half the sample had indicated some difficulty in Emotion, this was explored in more detail.

Table 9-5 *Age-at-Diagnosis and Emotion on MHSC*

Age-at-Diagnosis	Happy	Occasionally Fretful	Often Fretful
< 3 yrs n=13	77% (10)	23% (3)	0% (0)
4-6 yrs n=11	27% (3)	55% (6)	18% (2)
> 7 yrs n=27	37% (10)	51% (14)	11% (3)
Total n=51	45% (23)	45% (23)	10% (5)

significant at p <.05

The difference in emotional functioning according to Age-at-Diagnosis falls just short of significance (Chi Square 9.11; df=4; p =.058). The older the Age-at-Diagnosis, the greater is the likelihood of the person occasionally or often fretful.

9.7.2 Age-at-Diagnosis and Treatment Groups

Table 9-6 *Correlation matrix between Age-at-Diagnosis and MHSC*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
Sensation		.045	.048	.074
Mobility	.040	-.171	-.112	-.109
Emotion	.284	-.148	.566*	.114
Cognition	-.290	-.044	-.373	-.139
Self Care	-.255	-.178	-.284	-.219
Pain	-.331	-.149	.477*	.148
Total Score	-.143	-.097	-.037	-.067

significant at p<.05*

Positive significant correlations were only found in Group 3 between Age-at-Diagnosis and Emotion (p<.024) and Pain (p<.039) indicating that the older the subject at diagnosis, the greater the associated incidence of emotional difficulty and pain.

9.7.3 Years-since-Treatment

Table 9-7 *Correlation between Years-since-Treatment and MHSC*

	Sensation	Mobility	Emotion	Cognition	Self Care	Pain
Years	.431	.169	-.083	.104	.114	.177
	p<.002	p>.236	p>.563	p>.470	p>427	p>.215

n=51 significant p<.01

This table shows only one statistically significant correlation namely a moderate positive correlation between the number of Years-since-Treatment and impaired Sensation: The longer the number of Years-since-Treatment, the greater is the association in visual or hearing difficulty. The following table elaborates on the time parameter.

Table 9-8 *The implication of Years-since-Treatment on Sensation*

Years Since Tx	OK	Equip	Limited with Equip	Blind/ Deaf/ Mute
=/< 3 yrs n=20	95% (19)	5% (1)	0%	0%
3-5 yrs n=6	83% (5)	17% (1)	0%	0%
6-10 yrs n=8	25% (2)	50% (4)	12.5% (1)	12.5% (1)
> 10 yrs n=17	59% (10)	29% (5)	6% (1)	6% (1)
Total n=51	71% (36)	22% (11)	4% (2)	4% (2)

This table indicates that 71 % of the subjects have no deficits in sensation regardless of the number of Years-since-Treatment. However at six years and more post treatment, functional deficits became apparent. The small sample size limits the interpretation of the effects of treatment between the groups. Either deterioration with the passage of time or an improvement in treatment are possible reasons for this observed result.

9.7.4 Cognitive Outcome Measures and the MHSC

The neuropsychological test scores found to differentiate statistically significantly between the treatment groups were correlated with MHSC.

Table 9-9 *Correlation between MHSC and Cognitive Variables*

	FSIQ n=51	TVPS-VM n=43	AVLT n=37	VMI n=45	PURDUE n=46
MHSC Total Score	-.615 n=51 p=.000	-.430 n=43 p=.004	-.615 n=37 p=.000	-.517 n=45 p=.000	-.367 n=46 p=.012

significant at p <.05; p < .001

The statistically significant negative correlations indicate that the more impaired the scores on the tests of FISQ (prorated scores), TVPS (non motor) Visual Memory, Auditory Verbal Learning (AVLT), VMI (Beery) and Purdue Pegboard both hands, the more impaired is the health rating as measured by the total score on MHSC.

9.8. CORRELATION BETWEEN WPBIC AND MHSC

The positive significant correlation (r=.441; p<.009) between the total scores of the WPBIC (n=34) and the MHSC (n=51) indicated that there is an association between the frequency of scores endorsed in the domains of the two measures.

Specifically statistically significant correlations were shown:
Total score of WPBIC and sensation MHSC (r=.339; p<.050)
Total score WPBIC and emotion MHSC (r=.564; p<.001)
Total score WPBIC and cognition MHSC (r=.415; p<.015)

9.9. EDUCATIONAL STATUS ATTAINED

Changes in the Government's educational policy in the last five years have resulted in wide differences in the availability of education for children with special needs. Many of the children in normal school repeat standards because special class facilities are either not available in their particular school or they have to wait for a place in the special school. In addition to changes in educational policy, some parents are unwilling to

change their children to a special school because of the perceived social stigma. They may fail and yet be moved up to the next standard without having achieved the required pass mark.

The educational achievements of those subjects who have left school and those who are still attending school are shown in the tables below.

Table 9-10 *Educational Status Attained of Children and Adults*

	GROUP 1 n=12	GROUP 2 n=20	GROUP 3 n=19	ALL GROUPS n=51
Normal School	58% (7)	55% (11)	21% (4)	43% (22)
Normal School Special Class	-	10% (2)	21% (4)	12% (6)
Special School	33% (4)	5% (1)	42% (8)	25% (13)
Home	8% (1)	15% (3)	10% (2)	12% (6)
Too Young for School	-	15% (3)	5% (1)	8% (4)

This table indicates that almost half the children attending school are in a special class or a special school. There were more children in Group 3 attending special school compared with Groups 1 or 2.

9.10. CURRENT OCCUPATIONAL STATUS

Table 9-11 *The Frequency of Current Occupational Status of Adults and Young Adults Eligible to enter work market*

	GROUP 1 n=2	GROUP 2 n=11	GROUP 3 n=7	ALL GROUPS n=20
Tertiary Training	-	3	-	3
Working	1	5	3	9
Training Centre	-	1	2	3
Home D/G	1	2	2	5

D/G = Disability Grant

The small number of subjects and uneven distribution of patients in each group distort the treatment group comparison, but nonetheless highlight the positive finding that almost half the group are employed.

Tertiary Training: All the subjects are from Group 2 and their training ranges from a first year BA student to two students attending a technical training centre after passing standard 8.

Working Category: Group 2 has the highest number of employed subjects. Work categories range from domestic workers (Groups 1 and 3) to clerks and technical workers (Groups 2 and 3). In this latter category, two subjects achieved matriculation certificates.

Home: Disability Grant: All the subjects developed complications such as infection, repeated shunt revision, transient mutism or seizures.

9.11. SUMMARY

WPBIC

- There are no statistically significant difficulties in behaviour between the treatment groups, but trends showed that Group 3 had the highest incidence of problem behaviour. Specifically they had a high incidence of Immaturity. This was also a difficulty for Group 1. Disturbed Peer Relation was a domain of difficulty for Group 2 and 3, while Acting Out behaviour was present to a lesser or greater degree in all the children

- Age-at-Diagnosis was not statistically significantly correlated with problem behaviour

- A statistically significant negative correlation between prorated FSIQ and total score on WPBIC indicates that the lower the prorated FSIQ the higher the incidence of problem behaviours

MHSC

- Sixty four percent of the sample have a degree of functional morbidity, the cognition, emotion and mobility domains being he most frequently endorsed areas of difficulty

- Treatment effects between the groups were not statistically significant but trends showed that the mean total health rating score would increase as the adjuvants of RT and chemotherapy were added to the treatment protocols. Group 3 had the highest mean total score

- Age-at-Diagnosis was statistically significantly correlated with the domain of emotion. In Group 3, a statistically significant correlation was also found with emotion and pain, suggesting an association where the older the subject the greater is the incidence of occasional emotional difficulty and pain

- Years-since-Treatment correlated statistically significantly with MHSC only in the domain of sensation

- Statistically significant negative correlations were found between MHSC total score and FSIQ (prorated scores), non-motor Visual Memory (TVPS), verbal learning (AVLT), visual motor integration (VMI) and motor functions (Purdue Pegboard, both hands). There is evidence of an association between poor health rating score and difficulties in decreased cognitive functioning

- Forty three percent of the subjects (22 children) attend normal school

- Forty five percent of the subjects (nine young adults/adults) eligible to enter the work market are employed

CHAPTER 10

AGE-AT-DIAGNOSIS AND TIME-SINCE-TREATMENT

10.1. INTRODUCTION

The frequent confounding of the three age-related factors, Age-at-Diagnosis, Age-at-Testing and Time-since-Treatment, in studies of childhood brain tumours is a major obstacle to understanding their unique effects. To clarify these factors, the test measures which were found to differ significantly between the treatment groups were regarded as the most sensitive and were used to examine the effects of Age-at-Diagnosis and Years-since-Treatment.

10.2. AGE-AT-DIAGNOSIS AND INFLUENCE ON COGNITIVE VARIABLES

Table 10-1 *Effect of Age-at-Diagnosis on Cognitive Variables*

	< 4 YRS	4-6 YRS	> 7 YRS		
PRORATED FSIQ				**ANOVA (df = 2,48)**	
	n=13	n=11	n=27	**F**	**p-value**
X	74.53	71.36	79.07	.638	.532
SD	28.81	24.18	16.10		
TVPS VISUAL MEMORY (Percentile)				**ANOVA (df = 2,40)**	
	n=10	n=8	n=25	**F**	**p-value**
X	7.80	6.87	10.40	3.120	.055
SD	5.411	2.94	3.58		
AVLT – TOTAL (Raw Score)				**ANOVA (df = 2,34)**	
	n=6	n=7	n=24	**F**	**p-value**
X	45.33	34.42	41.58	.485	.619
SD	17.96	8.54	14.87		
VMI Beery (Percentile)				**ANOVA (df = 2,42)**	
	n=11	n=8	n=26	**F**	**p-value**
X	14.45	24.50	22.34	.453	.638
SD	22.34	30.25	26.11		
PURDUE PEGBOARD BOTH HANDS(Percentile)				**ANOVA (df = 2,43)**	
	n=10	n=9	n=27	**F**	**p-value**
X	21.00	38.88	24.07	1.508	.232
SD	16.63	34.07	23.57		

significant at p <.05

In this above table, there are no statistically significant differences between the Cognitive variables and the age groups when divided into the Age-at-Diagnosis groups. However, the non-motor Visual Memory (TVPS) outcome as indicated by the ANOVA outcome has not quite reached statistical significance at the <p.05 level. Inspection of the Scatterplot (Figure 10-1) shows a slight improvement with increasing age.

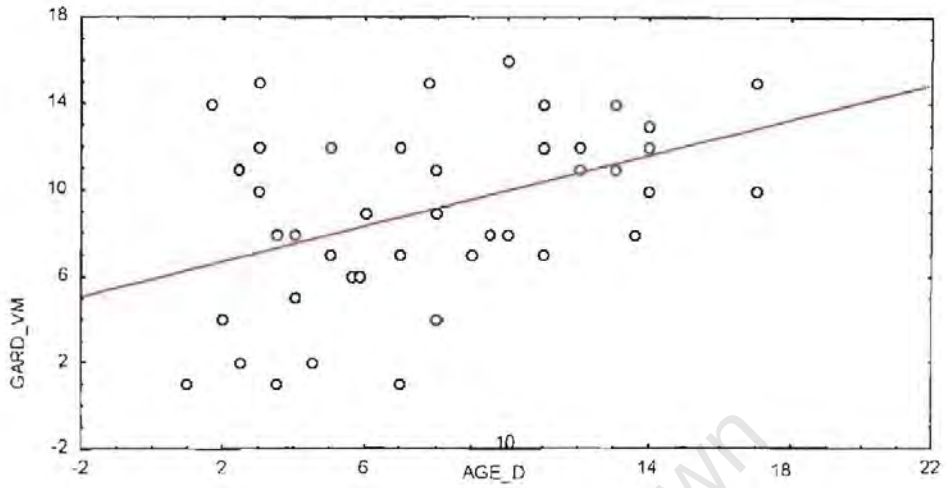


Figure 10-1 *Scatterplot of Age-at-Diagnosis versus TVPS Visual Memory*

10.3 YEARS-SINCE-TREATMENT AND INFLUENCE ON COGNITIVE VARIABLES

Table 10-2 *Effect of Years-since-Treatment on Cognitive Variables*

	< 4 YRS	4-6 YRS	7-10 YRS	10 + YRS		
PRORATED FSIQ					**ANOVA (df = 3,47)**	
	n=20	**n=6**	**n=8**	**n=17**	**F**	**p-value**
X	79.80	72.83	67.25	77.52	.826	.485
SD	17.14	22.11	20.43	22.30		
TVPS VISUAL MEMORY (Percentile)					**ANOVA (df = 3,39)**	
	n=15	**n=6**	**n=7**	**n=15**	**F**	**p-value**
X	8.60	6.50	8.85	10.86	1.858	.152
SD	2.84	4.88	4.01	4.70		
AVLT – TOTAL (Raw Score)					**ANOVA (df = 3,33)**	
	n=12	**n=3**	**n=8**	**n=14**	**F**	**p-value**
X	40.41	41.00	30.62	48.50	3.177	.036
SD	10.43	19.07	16.73	10.62		
VMI-Beery (Percentile)					**ANOVA (df = 3,41)**	
	n=16	**n=6**	**n=7**	**n=16**	**F**	**p-value**
X	39.31	15.33	6.42	10.62	5.902	.001
SD	28.49	23.90	12.24	17.03		
PURDUE PEGBOARD BOTH HANDS (Percentile)					**ANOVA (df = 3,42)**	
	n=17	**n=6**	**n=7**	**n=16**	**F**	**p-value**
X	31.76	20.00	15.71	27.50	.820	.490
SD	29.41	16.73	15.11	25.69		

significant at p <.05; p <.01

The above table shows a statistically significant difference in functioning on the AVLT–total score and Visual Motor Integration (VMI Beery) test scores and Years-since-Treatment. Inspection of the trends on the VMI (Table 10-2 and Figure 10-3) indicates that the trend of the percentile scores is to decrease with Years-since-Treatment. The AVLT results are harder to interpret. The scatterplot (Figure 10-2) suggests a slight increase with Years-since-Treatment, but the use of raw scores may

indicate that this increase is only a reflection of the expected mean increase from childhood to adulthood.

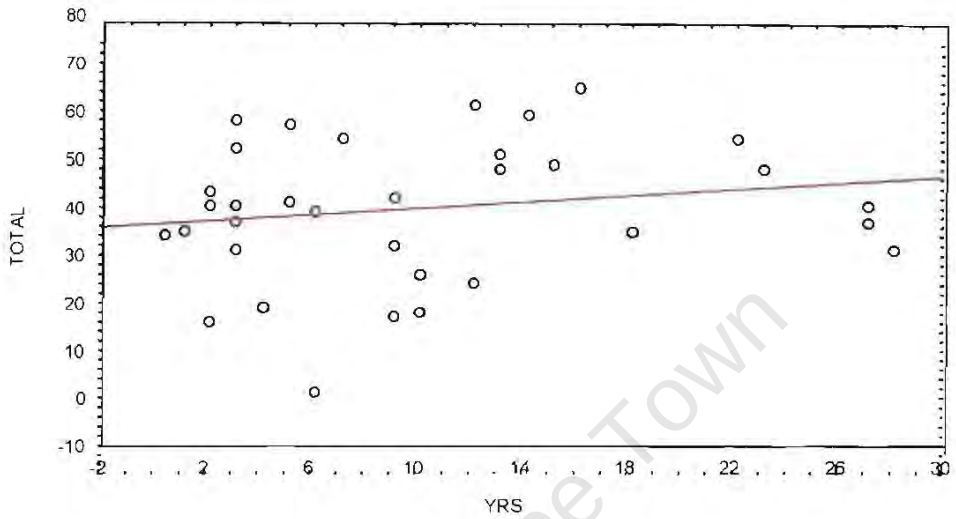


Figure 10-2 *Scatterplot of AVLT Total Number of Words Recalled versus Years-since-Treatment*

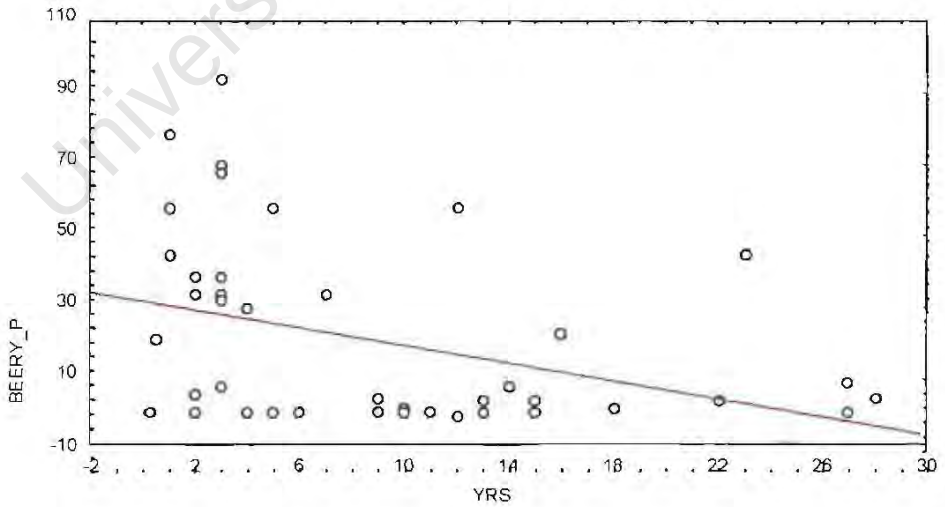


Figure 10-3 *Scatterplot of VMI (Beery) versus Years-since-Treatment*

10.4 INTERACTION OF AGE-AT-DIAGNOSIS AND YEARS-SINCE-TREATMENT

10.4.1 Medulloblastoma Group

To make the comparison with the analysis of Dennis *et al* (1996), the effect of Age-at-Diagnosis and Time-since-Treatment on prorated IQ variables was analysed on the medulloblastoma subjects treated by means of surgery and combinations of radiotherapy and chemotherapy.

The Age-at-Diagnosis categories were matched to those used by Dennis et al., (1996). This analysis was then repeated on the astrocytoma subjects treated by means of surgery only.

Table 10-3 *Summary of Age-at-Diagnosis, Years-since-Treatment and Prorated IQ test scores in Medulloblastoma Group*

	AGE-AT-DIAGNOSIS	YEARS – SINCE-TX	FSIQ	VIQ	PIQ
	0-3yr (n=10)				
X	2.58	8.96	72.10	74.90	71.70
SD	.82	6.01	21.80	20.39	21.15
	4-6yr (n=3)				
X	5.11	6.16	77.66	78.66	78.00
SD	.67	.75	33.47	34.67	33.86
	> 7yr (n=17)				
X	11.75	10.54	77.82	80.94	75.05
SD	3.04	8.50	17.85	18.43	17.03
	ALL GROUP (n=30)				
X	8.03	9.58	75.90	78.70	74.23
SD	4.96	7.43	20.20	20.18	20.97

TX = Treatment

This table shows the means and standard deviations for Years-since-Treatment and prorated IQ test scores (FSIQ, VIQ, PIQ) in the different Age-at-Diagnosis groups. The differences between the Medulloblastoma Group and the normative sample (a hypothetical population with a

mean=100, and sd=15) were significant for all IQ measures (FSIQ: t(29)=6.82, p < 0.0001; VIQ: t(29)= 5.79, p<0.0001; PIQ: t(29) = 7.00, p <0.0001).

The difference between mean VIQ and PIQ scores was however statistically significant (t (29) = 2.17, p < 0.04). From another aspect a greater number of the sample, 19 out of 30, had lower PIQ than VIQ scores although this difference was not statistically significant (x^2 (1) = 2.13, p > 0.14). The ANOVA between Age-at-Diagnosis groups and IQ variables failed to show any statistically significant differences (FSIQ; df = 2,27; F= 0.25; p > .779; VIQ; df=2,27; F=0.26; p>.767; PIQ; df=2,27; F= 0.12; p >.881).

Multiple regression analyses using Age-at-Diagnosis and Years-since-Treatment as predictor variables also failed to show any joint predictive relationship with the dependent variables (FSIQ; df = 2,27; F= 0.85; p > .436; VIQ df=2,27; F= 0.37; p > .692; PIQ df=2,27; F=0.82; p >.448)

A second calculation was done, limiting the sample to children under the age of 18 years at age-at-testing, this was done to match the Dennis *et al* (1996) analysis. Thus all adults were excluded.

Table 10-4 *Summary of mean Age-at-Diagnosis, Years-since-Treatment and Prorated IQ Test Scores on Medulloblastoma subjects age < 18 years*

	AGE-AT-DIAGNOSIS	YEARS SINCE-TX	FIQ	VIQ	PIQ
	0-3yr (n=9)				
X	2.48	7.96	72.55	75.00	72.88
SD	0.81	5.41	23.08	21.62	26.38
	4-6yr (n=3)				
X	5.11	6.16	77.66	78.66	78.00
SD	0.67	5.75	33.47	34.67	33.86
	> 7yr (n=8)				
X	10.06	3.78	73.55	76.20	76.30
SD	2.24	1.75	19.95	21.51	17.33
	ALL GROUP (n=20)				
X	5.90	6.02	73.55	76.20	73.30
SD	3.88	4.56	22.19	22.26	22.99

TX = Treatment

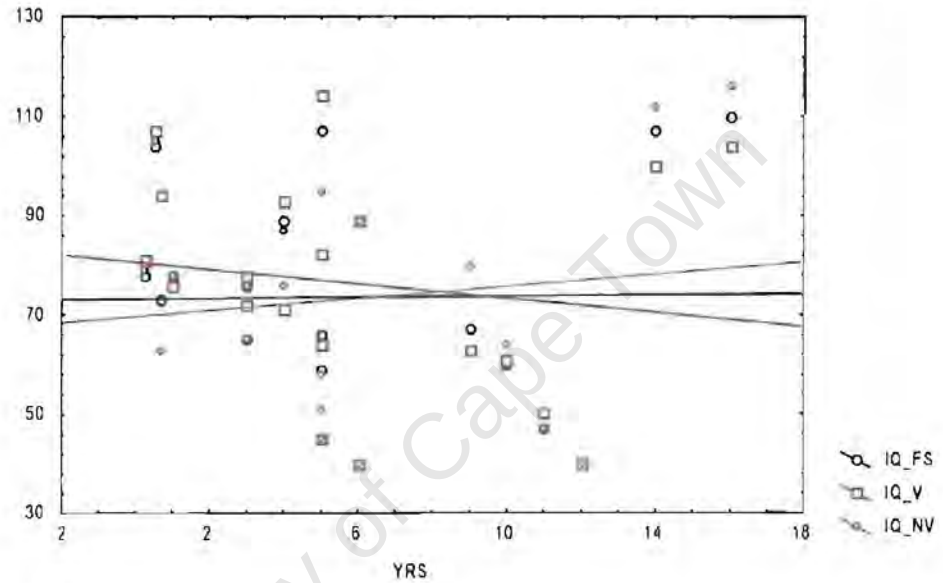
The summary table demonstrates that the differences between the mean VIQ and PIQ scores were not statistically significant ($t(19) = 1.05$, $p > 0.3$).

The ANOVA showed no statistically significant differences between the Age-at-Diagnosis groups on the prorated IQ variables (FSIQ; df=2, 17; F= 0.05; p > .945; VIQ; df =2, 17; F= 0.02; p > 970; PIQ; df=2,17; F = 0.29; p > .933).

Multiple regression analyses using Age-at-Diagnosis and Years-since-Treatment as predictor variables also failed to show any joint predictive relationship with the dependent prorated IQ variables (FSIQ; df= 2,17; F = 0.15; p > .859; VIQ ; df= 2,17; F = 0.28; p > .754; PIQ; df=2,17; F = 0.27; p > .765).

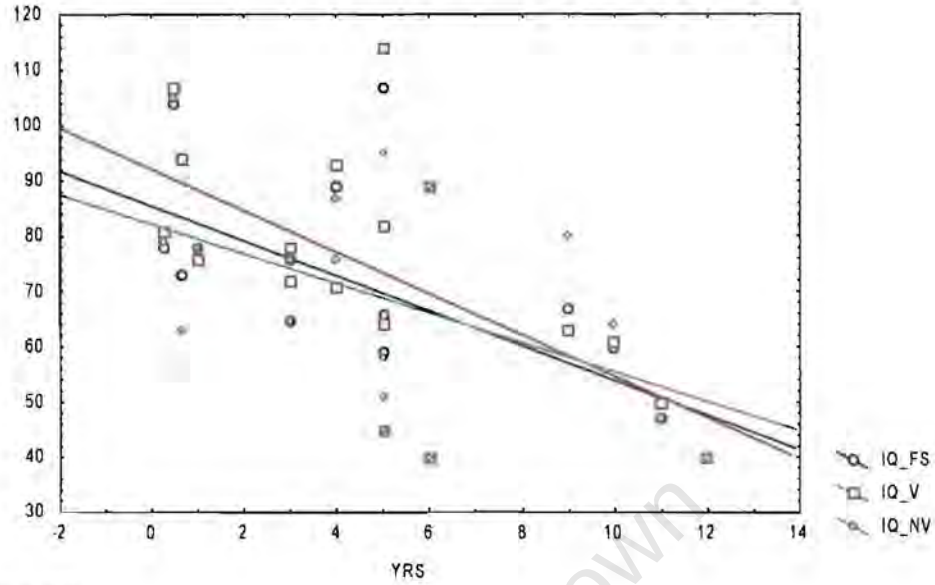
Inspection of the scatterplot of the mean prorated IQ scores and Years-since-Treatment (Figure 10-4) shows that two outlying cases are strongly influencing the results as they have unusually high prorated IQ scores for the Years-since-Treatment variable.

Based on the present data the two outlying cases reflect the clear large variation in prorated IQ scores at all points on the variable Years-since-Treatment. Therefore if some observations exert great leverage, there is justification for removing the outlying cases. In this way the picture changes as shown in the Figure 10-5.



n = 20

Figure 10-4 *Scatterplot of mean Prorated IQ scores versus Years-since-Treatment Medulloblastoma subjects*



n = 18

Figure 10-5 *Revised scatterplot of mean prorated IQ scores versus Years-since-Treatment on Medulloblastoma subjects*

In the revised sample of medulloblastoma subjects (n=18), multiple regression analyses indicate there are statistically significant predictive relationships with the dependent variables FSIQ and VIQ variables and Years-since-Treatment (FSIQ; df= 2,15; F = 3.94; p < .042; VIQ; df = 2,15; F = 4.82; p < . 024) No statistically significant relationship is shown on the PIQ and Years-since-Treatment (df = 2, 15; F = 2.70; p > .099), so that the longer the Years-since-Treatment the lower the FSIQ. The difference is apparent in VIQ and not PIQ. This finding needs to be made with caution as the heteroscedasticity of the scores has a potentially confounding effect on the results.

10.4.2 Astrocytoma Group

In order to ascertain whether the same IQ results can be obtained on the astrocytoma subjects treated by means of surgery only, the analysis was

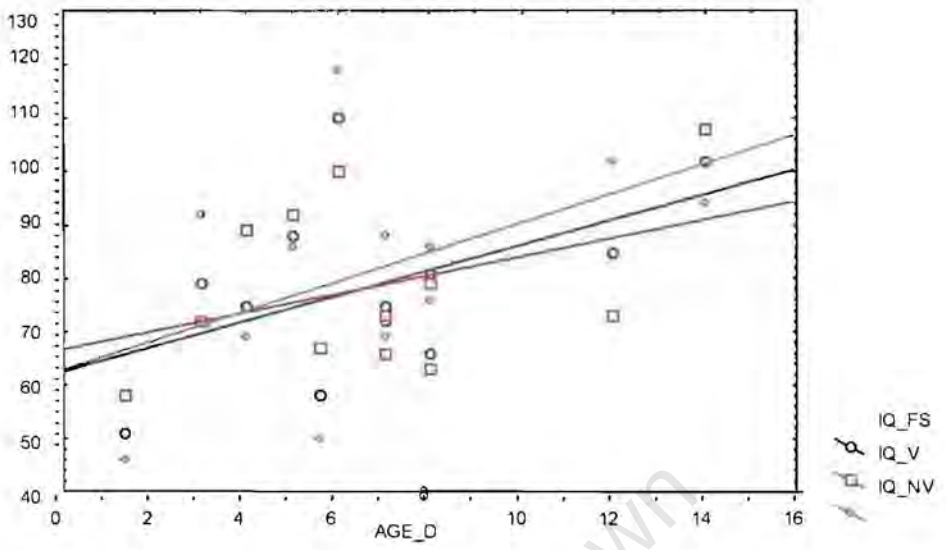
replicated on those subjects. All the children were younger than the age of 18 years at-testing.

Table 10-5 *Summary of Age-at-Diagnosis, Years-since-Treatment and prorated IQ Test Scores on children with Astrocytoma Tumours*

	AGE-AT-DIAGNOSIS	YEARS SINCE-TX	FSIQ	VIQ	PIQ
			0-3yr (n=2)		
X	2.16	8.00	65.00	65.00	69.00
SD	1.18	7.07	19.79	9.89	32.52
			4-6yr (n=4)		
X	5.15	4.75	82.75	87.00	81.00
SD	0.86	6.84	21.92	14.18	29.29
			> 7yr (n=6)		
X	9.33	2.66	80.16	77.00	85.83
SD	2.94	0.51	12.60	16.21	11.94
			ALL GROUP (n=12)		
X	6.74	4.25	78.50	78.33	81.41
SD	3.55	4.63	16.74	15.59	20.82

TX = Treatment

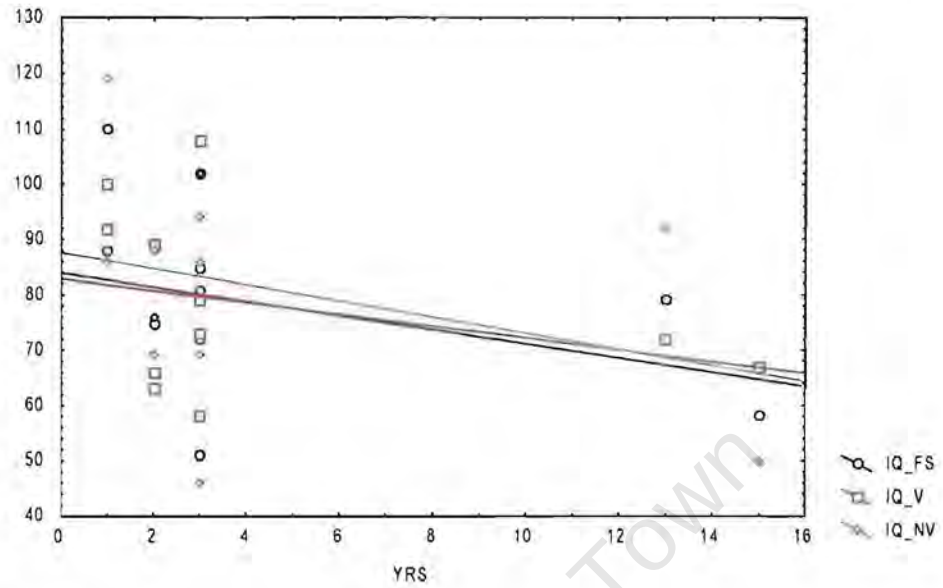
This table shows that the differences between the Astrocytoma group and the normative sample (a hypothetical population with a mean = 100, and standard deviation = 15) were significant for all measures (FSIQ: $t(11) = 4.96$, $p < .0001$; VIQ: $t(11) = 5.00$, $p < .0001$; PIQ: $t(11) = 0.61$, $p < .0001$). The difference between VIQ and PIQ scores, was not statistically significant ($t(11) = 0.61$, $p > .55$)



n=12

Figure 10-6 *Scatterplot of mean prorated IQ scores versus Age-at-Diagnosis in Astrocytoma Group*

This figure shows that there are no statistical significant differences between Age-at-Diagnosis and the prorated IQ variables (FSIQ; df = 2, 9; F = 0.77; p > .488; VIQ; df= 2,9; F = 1.49; p > .655; PIQ; df = 2,9; F= 0.44, p > .656). The scatterplot in the figure 10-6 indicates the IQ trends that the younger the Age-at-Diagnosis the lower the prorated FIQ and the older the Age-at-Diagnosis the better the prorated IQ score. This is a tentative assumption as the sample size is small and the result has not been statistically confirmed.



n=12

Figure 10-7 *Scatterplot of Astrocytoma Group showing Years-since-Treatment and mean prorated IQ Scores*

In this figure correlations between any of the prorated IQ measures and Years-since-Treatment showed no significant relationship: FSIQ (r= -.356; p > .257); VIQ (r= - .318; p >. 314); PIQ (r= -.324; p=<.304). Multiple regression analysis using Age-at-Diagnosis and Years-since-Treatment as predictor variables failed to show any joint predictive relationships with the dependent IQ measures. FSIQ (df = 2, 9: F = 2.01; p > .188); VIQ (df = 2,9; F = 1.18; p > .349); PIQ (df = 2,9; F = 1.63; p > .247). Unfortunately the small size of the sample limits the results.

10.5. SUMMARY OF AGE-AT-DIAGNOSIS AND YEARS-SINCE-TREATMENT FINDINGS

- A statistically significant effect was found on Years-since-Treatment and Visual Motor Integration (VMI) Beery scores. The VMI scores tend to decrease or plateau with time as the child gets older.

- There was also a statistically significant effect found on Years-since-Treatment and AVLT total scores. As the raw scores were used this may reflect the expected increase from childhood to adulthood.

- An effect which did not quite achieve statistical significance was found on Age-at-Diagnosis and immediate non-motor Visual Memory (TVPS).

In the exploration of the interaction of Age-at-Diagnosis and Years-since-Treatment on the medulloblastoma and astrocytoma tumour groups:

- Medulloblastoma group – the entire group: Multiple regression analysis using Age-at-Diagnosis and Time-since-Treatment on the prorated IQ variables did not reveal a predictive relationship on the prorated IQ variables.

- Medulloblastoma group restricted to those under age 18 years at-testing: The correlation between Age-at-Diagnosis and Years-since-Treatment was negative and of moderate size. The younger the Age-at-Diagnosis the longer the Time-since-Treatment.

- Medulloblastoma group restricted to those under age 18 years at-testing. Multiple regression analysis indicated a statistically significant difference in Years-since-Treatment on prorated FSIQ and VIQ but not on PIQ: The longer the Years-since-Treatment the lower the prorated FSIQ and VIQ.

- Astrocytoma group all of whom were younger than the age of 18 years at-testing. Multiple regression analyses using Age-at-Diagnosis and Years-since-Treatment as predictor variables failed to show any joint predictive relationship with the dependent IQ measures. The correlation between Age-at-Diagnosis and Years-since-Treatment was negative, non-significant and of a moderate size. The small sample size limits the results.

CHAPTER 11

MEDULLOBLASTOMA TUMOURS

11.1 INTRODUCTION

In order to explore which factors were influencing the subjects treated by means of surgery, radiotherapy and chemotherapy, post hoc analysis was done on all the children diagnosed with medulloblastoma tumours. A total of thirty subjects was extracted from the sample (see Appendix A). Of these, eleven children were treated with Surgery and Radiotherapy (S+RT) and were named Group 4. The remaining nineteen medulloblastoma subjects were from the original Group 3, treated by means of Surgery, Radiotherapy and Chemotherapy (S+RT+C).

The following tables describe the two medulloblastoma treatment groups according to demographic characteristics, age and years since treatment, occupation as a measure of socioeconomic status and psychosocial adversity. Pre-treatment variables as well as intra-operative and post- operative complications are also described and analysed.

Although the full radiotherapy and chemotherapy treatment details are given in the appendix (Appendix A) a summary of the radiotherapy treatment protocols of the medulloblastoma subjects is also given.

In an attempt to try and identify the effect of the inclusion of chemotherapy on cognitive outcome on the medulloblastoma subjects the prorated FSIQ scores were used as a basis for comparison between Group 4 (S +RT) and Group 3 (S+RT+C).

11.2 DESCRIPTION OF MEDULLOBLASTOMA SAMPLE

11.2.1 DEMOGRAPHY

Table 11-1 Observed Frequencies of Gender, Race and Language

	Group 3 S+RT+C (n=19)	**Group 4 S+RT (n=11)**	**Pearson Chi-square**
	Gender		.095694; df=1; p=.757060
Male	58% (11)	64% (7)	
Female	42% (8)	36% (4)	
	Race		1.40931; df=2; p= .494282
Coloured	79% (15)	64% (7)	
White	11% (2)	27% (3)	
Black	11% (2)	9% (1)	
	Language		.913297; df=2; p = .633404
English	47% (9)	36% (4)	
Afrikaans	42% (8)	55% (6)	
Xhosa	11% (2)	9% (1)	

The above table shows that there are no significant differences at the 5% level of significance between the treatment groups in terms of gender, race or language.

11.2.2 AGE AND YEARS – SINCE - TREATMENT

Table 11-2 Age-at-Diagnosis, Age-at-Testing and Years-since-Treatment, expressed in years.

	Group 3 S+RT+C (n=19)	Group 4 S+RT (n=11)	t-value	df	p
	Age-at-Diagnosis		**-0.41179**	**28**	**.683632**
X	7.68	8.46			
SD	4.81	5.47			
Range	0.9 – 17.2	1.6 – 17			
	Age-at-Testing		**-1.39581**	**28**	**.173742**
X	15.29	20.68			
SD	8.24	13.07			
Range	3.7 – 39.8	4.08 – 40.75			
	Years-since-Treatment		**-1.55979**	**28**	**.130042**
X	7.57	12.00			
SD	5.92	9.57			

The above table indicates that there are no significant differences, at the 5% level of significance, between the medulloblastoma subjects treated by means of Surgery+RT (Group 4) and Surgery+RT+C (Group 3) in terms of Age-at-Diagnosis, Age-at-Testing and Years-since-Treatment.

11.2.3 OCCUPATION AS A MEASURE OF SOCIO-ECONOMIC-STATUS AND PSYCHOSOCIAL ADVERSITY

Occupational status and Psychosocial Adversity were classified according to the criteria explained in Chapter 7.

Table 11-3 Occupational Status in Subjects with Medulloblastoma Tumours.

	GROUP 3 S+RT+C (n=19)	GROUP 4 S+RT (n=11)	Pearson chi square 3.11688; p = .538462
Professional & Managerial	10% (2)	18% (2)	
Middle White Collar	16% (3)	36% (4)	
Manual, Foreman & Skilled	42% (8)	18% (2)	
Routine Non Manual	26% (5)	18% (2)	
Unskilled Manual & Menial	5% (1)	9% (1)	
	Median = 3	Median = 2	

The above table indicates that there are no statistical differences, at the 5% level of significance, between the medulloblastoma tumour groups treated by means of Surgery + RT (Group 4) and Surgery RT+C (Group 3) according to occupational status. Little difference is shown in the median scores.

Table 11-4 Psychsocial Adversity of Subjects with Medulloblastoma Tumours.

	Group 3 S+RT+C n = 19	Group 4 S+RT n = 11
Large family size	11% (2)	(18%) 2
Overcrowding	11% (2)	(18%) 2
Unskilled/ Unemployed	37% (7)	(45%) 5
Maternal Education < Std 6	47% (9)	(27%) 3
Mother Psychiatric	5% (1)	0%
Father Psychiatric	11% (2)	(18%) 2
Single Parent	11% (2)	(18%) 2
Disharmony in home	16% (3)	(9%) 1
Ill health either parent	0%	0%
Nutrition	26% (5)	(27%) 3
	Median Psychosocial	Adversity Score
	2	2

The above table shows that according to the median psychosocial adversity scores there is little difference between the two groups. A trend is shown for Group 3 to have more subjects with mother's who have less than a standard six or grade eight level of education.

11.3 PRETREATMENT VARIABLES

11.3.1 Presenting Symptoms

These are fully described in Chapter 7 and there is little difference between the groups.

11.4 TREATMENT

The treatment variables explored in relation to the medulloblastoma tumour subjects are shunts, the extent of the surgical resection, intra-operative and post-operative complications and a description of sites range and mean duration of radiation treatment.

Table 11-5 The Occurrence of Shunts and / or EVD expressed in Percentages

	Group 3 S+RT+C (n=19)	**Group 4 S+RT (n=11)**	**Pearson Chi Square**
	SHUNT / EVD		**1.40931; df=2; p=.494282**
SHUNT	89% (17)	64% (7)	
NO SHUNT	O%	27% (3)	
EVD + SHUNT	11% (2)	9% (1)	

As the majority of the children in both groups needed shunting, the presence or absence of a shunt and / or EVD is not significantly different between the treatment groups.

However the proportion of children in Group 4 who did not need a shunt is higher than that of Group 3, where all the subjects either had a shunt or a drain. In addition, the drains of the two children in Group 3 were replaced by shunts whereas the drain of the child in Group 4 was removed and did not necessitate replacement with a shunt. Thus children in Group 4 have a lower incidence of clinical signs of hydrocephalus than the children Group 3.

Inspection of the prorated FSIQ outcome in the three subjects who did not need a shunt in Group 4 (FSIQ=110, 83, 79) indicates that the one subject attained the highest score in the group and the other two subjects have scores close to the median FSIQ of 83. Other outcome measures of importance in the three subjects is that they have the longest Time-since-Treatment (16 years, 28 years and 27 years respectively). The mean Time-since-Treatment for the groups is 12 years. Thus, subjects that do not have clinical signs of hydrocephalus at diagnosis, necessitating the insertion of a shunt appear to have a better outcome in terms of cognitive functioning and mortality as shown by Time-since-Treatment variable, than those subjects in Group 3. Unfortunately the small number of subjects precludes a sounder interpretation of the finding.

Table 11-6 The Extent of the Surgical Resection

	Group 3 S+RT+C (n=19)	**Group 4 S+RT (n=11)**	**Pearson Chi Square**
	EXTENT OF SURGERY		**3.58852;df=1;p=.058183**
TOTAL	32% (6)	73% (8	
SUB TOTAL	68% (13)	27% (3)	

The extent of the surgical resection is just short of significance at the 5% level of significance. Group 4(S+RT) have a higher incidence of total surgical resections as compared to Group 3 (S+RT+C) who have a higher incidence of sub total resections.

As Grill *et al.,* (1999) found that an incomplete surgical resection strongly correlated with the radiation dose and was thus associated with a poorer intellectual outcome the mean prorated FSIQ scores of the two groups was explored.

Table 11-7 Prorated Mean FSIQ Scores According to Extent of Surgical Resection.

	TOTAL RESECTION	SUB TOTAL RESECTION
GROUP 4 (S+RT) n=11	FSIQ = 90.87 (n=8) Range 65-110	FSIQ = 74 (n=3) Range 60 – 83
GROUP 3 (S+RT+C) n=19	FSIQ = 67.5 (n=6) Range 45-89	FSIQ = 71 (n=13) Range 40 – 105
TOTAL n=30	FSIQ = 79.15 (n=14)	FSIQ = 72.5 (n=16)

Inspection of the prorated FSIQ outcome scores shows that Group 4 subjects, who had total surgical resections treated by means of surgery and radiotherapy are functioning in the average range of intelligence. The prorated FSIQ scores of the subtotal surgical resection subjects (Group 3 & 4) as well as the prorated FSIQ scores of the children who had total surgical resections (Group 3) shows that they are functioning in the borderline to mild mental retardation range of intelligence. An unexpected finding is that the Group 3 subjects who had total surgical resections have the lowest prorated FSIQ scores.

One suggests that the retrospective nature of the study over a lengthy twenty eight year period in which improvement in diagnostic techniques such as CT scan and MRI as well as surgical techniques are exerting an immeasurable cohort effect on the results. CT scan was developed in the 1970's (Lindsay *et al.,* 1998). MRI is more accurate in measuring the amount of residual tumour after surgical resection. This technique has only been available to Groote Schuur and Red Cross Hospitals in the last ten years. Within the entire sample of medulloblasoma subjects, only one child (Group 4), had a post operative MRI of the head.

Table 11-8 Summary of Frequency of Intra-Operative and Post-Operative Complications

	GROUP 3 S+RT+C (n=19)	GROUP 4 S+RT (n=11)
	INTRA-OPERATIVE COMPLICATIONS	
	5% (1)	0%
	POST-OPERATIVE COMPLICATIONS	
Infection	26% (5)	9% (1)
Mutism	11% (2)	9% (1)
Seizures	5% (1)	0%

The above table shows that Group 3 has a higher incidence of children who developed post operative infections (shunt infections = 3; meningitis = 2) compared to Group 4, in which one child had a shunt infection. This finding possibly supports the notion that Group 3 has an higher incidence of hydrocephalus.

Table 11-9 Sites of Radiation Treatment, Range of Radiation Dose and Mean Duration of Treatment

	GROUP 3 S+RT+C (n=19)	GROUP 4 S+RT (n=11)
WHOLE BRAIN	20 – 40 Gy	20 – 35 Gy
SPINAL	14 – 42 Gy	20 – 47 Gy
POSTERIOR FOSSA	10 – 58 Gy	10 – 42 Gy
CRIB BOOST	24 – 32 Gy	32 Gy
DURATION OF TREATMENT	7 weeks	5.45 weeks

The above Table indicates that it is difficult to compare the dose of radiotherapy as the protocols changed over the twenty eight year period of the study. However, inspection of the range of radiotherapy doses shows that Group 3 had a slightly broader and higher range of radiation treatment compared to Group 4. In Group 4, one child was treated with radiotherapy to the Posterior fossa area only (Appendix A case 27) whereas all the children in Group 3 received radiotherapy which included the Posterior Fossa site. Only one child in Group 4 had a boost of radiotherapy to the cribriform plate (case

no 9) compared to three children in Group 3 (Appendix A). Thus Group 3 children appear to have had a higher dose of radiotherapy treatment than those in Group 4.

The average duration of the radiotherapy treatment was slightly shorter for Group 4 children than those children in Group 3. All the subjects in both groups completed their treatment.

11.5 COGNITIVE FUNCTIONING

11.5.1 Prorated FSIQ Scores

The prorated FSIQ scores were used to explore the effects of treatment on cognitive functioning. These scores were used as there was no missing data and other calculations had been done using prorated FSIQ scores on the Age and Time variables (see chapter 10). A description of the prorated FSIQ scores obtained between the groups on the relevant IQ test measures is given below.

Table 11-10 Description mean Prorated FSIQ Scores According to Type of IQ Test Administered

	GROUP 3 S+RT+C n=19	**GROUP 4 S+RT n=11**
	FSIQ	**FSIQ**
SAWAIS	73.5 (n=4)	92 (n=7)
RANGE	53-105	73-110
SSAIS-R	63.5 (n=9)	77.3 (n=3)
RANGE	40-89	60-107
GRIFFITHS	82.6 (n=3)	73 (n=1)
RANGE	66-104	

A trend is shown for Group 3 (S+RT+C) subjects to have lower prorated FSIQ scores than Group 4 subjects. The small number of children tested on the Griffiths precludes further interpretation.

11.5.2 Cognitive Differences Between The Treatment Groups

A t-tests was applied to try and identify a significant statistical difference between the prorated FSIQ means of the medulloblastoma tumour subjects, Group 3 treated by means of S+ RT + C and Group 4 treated by means of S+RT.

The t-test assumes that the two groups are representative of a larger, inclusive population of subjects. In statistical terms a common variance between individual observations in each sample is present.

Table 11- 11 t-Test on Mean Prorated FSIQ scores : Two –Sample Assuming Equal Variance.

	GROUP 3 S+RT+C (n=19)	GROUP 4 S+RT (n=11)
Mean FSIQ	69.89474	86.27273
Variance	374.9883	322.0182
Pooled Variance	356.0704	
Hypothetical Mean Difference	0	
df	28	
t Stat	-2.2909	
P (T< t) two tail	0.029703	
T Critical two tail	2.048408	

The above Table shows that at the 3% level of significance the medulloblastoma subjects treated by means of Surgery and Radiotherapy have significantly higher prorated FSIQ scores than those treated by means of Surgery, Radiotherapy and Chemotherapy.

11.6 PRORATED FSIQ AND SES

The ANOVA statistic was computed to assess the extent to which each of the categorical variables, SES and Group (treatment, Group 3 treated by means of

Table 11-13 Within cell Regression (ANOVA) to investigate the extent of SES on Prorated FSIQ

	Sum of Squares	df	Mean Square	F	p level
Effect	735.1445	1	735.1445	2.149353	.154181

The above calculation shows that the means are not significantly different at the 5% level of significance. In other words SES is not found to significantly influence prorated FSIQ given the effect of the GRP (treatment) variable.

11.7 SUMMARY

Description of Sample

- There are no significant differences between Group 3 and Group 4 subjects in terms of gender, race, language, Age-at-Diagnosis, age-at-testing, and years-since-treatment.

- There are no significant differences between the treatment groups according to SES.

- According to psychosocial adversity measures a trend is found for Group 3 (S+RT+C) medulloblastoma subjects to have a higher percentage of mother's with less than a standard six or grade eight, level of education than Group 4.

Treatment

- There are no significant differences between the treatment groups in terms of the presence of a shunt or external ventricular drain. However the proportion of children in Group 4 who do not have shunts is higher than that of Group 3. Thus, children in Group 4 have a lower incidence of clinical signs of hydrocephalus than those in Group 3. In addition, subjects that do

S+RT+C and Group 4 treated by means of S+RT) discriminate between the medulloblastoma cases assessed on prorated FSIQ scores.

The mean prorated FSIQ of both the Groups assessed on each variable are used in calculating the test statistic.

Table 11-12 ANOVA Results on prorated FSIQ scores

Group
Group 3 S+RT+C mean FSIQ = 69.89474; sd = 3
Group 4 S+RT mean FSIQ = 86.27273; sd = 2.636364

ANOVA Results: FSIQ

	(F/R)	Df	F	p
SES	Fixed	1	3.292235	0.080735
GRP	Fixed	1	4.320748	.04728

The above table shows that for SES the mean prorated FSIQ scores are only significant at the 9% level of significance and conclude that the means are not significantly different at the 5% level of significance.

For GRP (treatment group) a significant difference is found at the 5% level of significance.

In other words both SES and GRP (treatment group) are found to significantly discriminate between the cases assessed on the prorated FSIQ measures but to different degrees of significance.

A further analysis was done to investigate the extent to which SES is a significant discriminator given the 5% significant effect on FSIQ.

not have clinical signs of hydrocephalus at diagnosis, necessitating the insertion of a shunt appear to have a better outcome in terms of cognitive functioning and mortality than those with hydrocephalus. Unfortunately this finding needs to be verified on a larger sample.

- The extent of the surgical resections between the Groups is just short of significance at the 5% level. Group 4 (S+RT) children have a higher percentage of total resections compared to Group 3 (S+RT+C) children who have a higher percentage of sub total resections.

- The subjects in Group 3 appear to have been treated with a higher dose of radiotherapy according to the range and site of treatment than Group 4 subjects.

Cognition and Treatment

- An inconsistent pattern of prorated FSIQ scores was found according to the extent of the tumour resection between and within the treatment groups. However on inspection of the scores of all the medulloblastoma subjects little difference was shown between prorated FSIQ scores according to the extent of the surgical resection. The group as a whole is functioning in the borderline range of intellectual functioning. One suggests that the retrospective nature of the design is exerting some degree of a cohort effect on the results.

- A statistically significant difference in prorated FSIQ scores was found between the groups according to the treatment of S+RT (Group 4) and S+RT+C (Group 3). Group 4 subjects have a higher level of FSIQ functioning and are functioning in the low average range of intelligence whereas Group 3 subjects are functioning on the cusp of the borderline/ mental retardation range of intelligence.

- The ANOVA was calculated to assess the extent to which SES and treatment discriminated between the medulloblastoma treatment groups on prorated FSIQ scores. SES was not found to significantly influence the prorated FSIQ score given the effect of the treatment variable.

- One thus concludes that in the sample of medulloblastoma subjects, the children in Group 4 are functioning better in terms of cognitive outcome than the children in Group 3. This is possibly due to :

  the presence of a higher incidence of clinical signs of hydrocephalus, the higher dose of radiotherapy and the addition of chemotherapy in the children in Group 3.

  However the effects of Age–at-Diagnosis, Age-at-Testing and Time-since-Treatment need further exploration.

CHAPTER 12

PREDICTORS OF OUTCOME

12.1 INTRODUCTION

A series of multiple regression analyses were carried out in order to build a Model that would predict outcome variables from a number of predictor variables. Since there were multiple outcome variables, Principal Component analysis was first used to simplify the set of outcome variables.

12.2 PRINCIPAL COMPONENT ANALYSES

TVPS (non motor visual memory), AVLT total score, Visual Motor Integration (Beery), Purdue Peg Board (both hands) variables that had proven sensitive to differences between the treatment groups plus FSIQ were included in the Principal Component Analyses. Tables 12-1 and Figure 12-1 as indicated below, show the Principal Component Analysis which yielded two variables.

Table 12-1 Summary analysis of Principal Components on dependent variables

		% Total	Cumulation	Cumulation
Component Variable	Eigenval	Variance	Eigenval	%
1	2.8305	56.6118	2.8305	56.6118
2	1.0776	21.5537	3.9082	78.1656
3	.5299	10.5980	4.4381	88.7637
4	.3406	6.8123	4.7788	95.5760
5	.2211	4.4239	5.0000	100.0000

Table 12-1 and Figure 12-1 indicate that using Kaiser's rule (eigen value >1) it will be appropriate to extract 2 components. Component 1 accounts for 56% of the total variance and Component 2 accounts for 21% of the total variance.

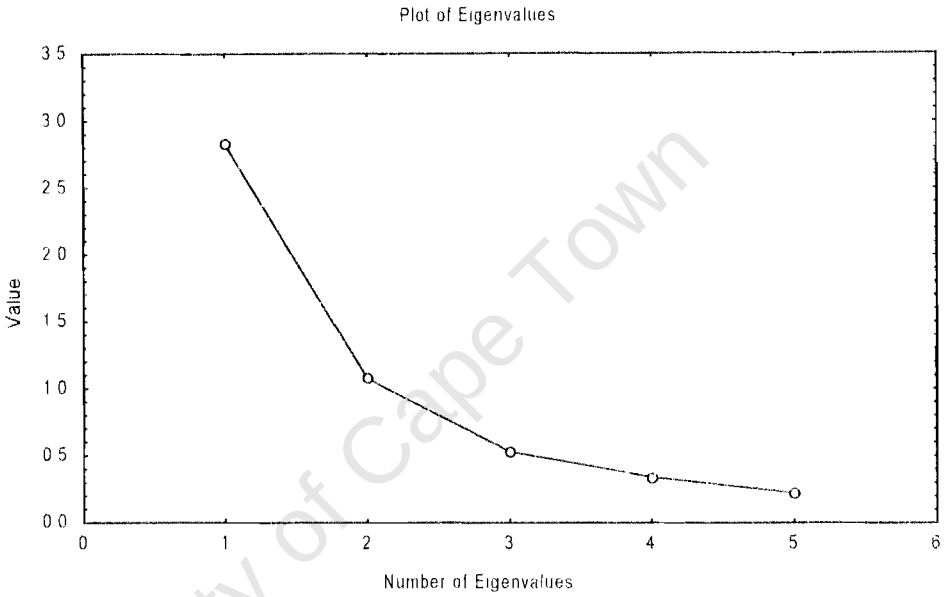


Figure 12-1 Scatterplot of Eigen Values

Table 12-2 Varimax Normalised Rotation of Components

	COMPONENT 1	**COMPONENT 2**
FIQ	.7465	.4705
TVPS	.9309	.0252
AVLT-TOTAL	.8407	.2293
VMI	.1568	.8749
Purdue --both hands	.1703	8267
Expl. Var	2.1845	1 7237
Prp. Total	.4369	.3447

Table 12-2 indicates that component 1 is best defined by FSIQ, TVPS (visual memory) and AVLT- total score and appears to represent a global outcome based on intelligence and memory.

Component 2 is best thought of as the composite of VMI (Beery) and Purdue pegboard (both hands) and appears to represent a specific visual motor outcome.

12.3. MULTIPLE REGRESSION ANALYSIS

Stepwise regression analyses were conducted, using the STATISTICA programme to determine which independent variables would predict these two components. The forward entry method was used.
The independent variables were Treatment Groups (in three categories), Tumour Type (astrocytoma and medulloblastoma), Age-at-Diagnosis, Years-since-Treatment, Age-at-Testing, SES and repeated Shunt Revision.

- **PC1**

Table 12-3 Summary of Step Wise Multiple Regression Analysis on PC1

	Multiple R	Multiple R-square	R-square Change	F – to Entr/rem	p-level
SHUNT REVISION	.5719	.3271	.3271	14.5866	.0007
SES	.7504	.5632	.2360	15.6763	.0004
YEARS	.7759	.6020	.0388	2.7323	.1099
TUMOUR TYPE	.8165	.6667	.0646	5.2353	.0301

significant at $p < .05$; $p < .01$; $p < .001$

Table 12-4 Regression Summary for PC1

	Beta	St. Err. of Beta	B	St. Err. of B	t(27)	p-level
Intercpt			3.5055	.5110	6.8599	.0000
Shunt RV	-.5270	.1170	-1.4679	.3259	-4.5030	.0001
SES	-.5845	.1164	-.5459	.1087	-5.0210	.0000
YRS	.3365	.1285	.0460	.0175	2.6182	.0143
Tumor Type	-.3010	.1315	-.2136	.0933	-2.2880	.0301

significant at p<.05; p<.01; p<.001

The best model for predicting PC1 as shown in Tables 12-3 and 12-4 was found to be a model employing the indicators SES, Tumour Type, Years-since-Treatment and Repeated Shunt Revision.

The regression calculation for PC1 as in Table 12-4 (R =.81651914 R2=.66670350, Adjusted R2=.6173264; F(4.27)=13.502 p<.00000; Std Error of estimate: .63554) explained 61% of the variance in the dependent variable, which is considered a good outcome. Note the association with SES is negative because the Groups with the highest occupational status have the lowest numbers (e.g. 1=professional status, 5=unskilled manual status). Thus a high PC1 correlates with increasing years since treatment, type of tumour, absence of shunt revision and high SES.

- **PC2**

The best model for predicting PC2 is a model employing Years-since-Treatment (R=.52555078 R2=.27620362, Adjusted R2=.25207707; F(1.30)=11.448; p<.00201; Std Error of estimate: .8660). Table 12-5 below reports the results for the full model. In this instance the equation

explained 25% of the variation which is considered an acceptable outcome but not as high as that shown in PC1.

Table 12-5 Summary of Step Wise Multiple Regression on PC2 Years-since-Treatment

	Multiple R	Multiple R-square	R-square change	F – to Entr/rem	p-level
YRS	.5255	.2762	.2762	11.4481	.0020

significant at $p < .01$

Table 12-6 Regression Summary for PC2 (Years-since-Treatment)

	Beta	St. Err. of Beta	B	St. Err. of B	t(27)	p-level
Intercpt			.7043	.2446	2.8793	.0072
Years	-.5255	.1553	-.0701	.0207	-3.3835	.0020

The regression summary Table 12-6 shows a large St. Error as the scores on PC2 were widely scattered.

Table 12-7 Regression Summary for PC2 (Tumour Type and SES)

	Beta	St. Err. of Beta	B	St. Err. of B	t(29)	p-level
Intercpt			1.2399	.6120	2.0259	.0520
Tumour Type	-.3955	.1700	-.2738	.1177	-2.3257	.0272
SES	-.1405	0170085	-.1280	.1549	-.8260	.4155

When Tumour Type and SES were used as predictors (R=.40856365 R2=.16692425, Adjusted R2=.10947075, F(2,29)=2.9054, p<.07078, Std error of estimate:.94561) only Tumour Type was significant, but SES is not, as shown in Table 12-7.

Table 12-8 Regression Summary for PC2 (Tumour Type and Years-since-Treatment)

	Beta	St. Err. of Beta	B	St. Err. of B	t(29)	p-level
Intercpt			1.0010	.3573	2.8016	.0089
Tumour Type	-.1941	.1711	-.1343	.1184	-1.1346	.2658
Years	-.4422	.1711	-.0590	.0228	-2.5846	.0150

However Tumour Type and Years-since-Treatment are strongly correlated (>0.4, multicollinearity) and it is difficult to decide which has priority over the other (R=.5540673, R2=.30696778, Adjusted R2=.25917245, F(2,29)=6.4225, P<.00491, Std Error of estimate:.86248) as shown in Table 12-8.

CHAPTER 13

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

13.1. REPRESENTATIVENESS OF THE SAMPLE

The incidence of posterior fossa tumours at Groote Schuur and Red Cross Hospitals is comparable with that in international studies. However, the lack of a uniformly accepted classification system of brain tumours has led to a disparity both in the incidence rate of different types of brain tumours and in the impact of treatment on children with brain tumours (Becker, 1985; Giles, 1985; Miller *et al.,* 1995).

In accordance with other findings, medulloblastoma was found to be the most common posterior fossa brain tumour in the sample (Bloom *et al.,* 1990; Cohen and Duffner, 1984; Humphreys, 1982; Johnson *et al.,* 1994; Silverberg *et al.,* 1981) The 44% incidence of medulloblastoma tumours in the identified sample of 174 posterior fossa brain tumours is reported in other studies (Bierbrauer *et al.,* 1989; Bloom *et al.,* 1990; Halperin *et al.,*1994). The relatively high (30%) incidence of brain stem glioma tumours within the sample reflects the confusion surrounding the diagnosis which has resulted in incidence rates varying from 10% to 25% (Hoffman & Goumnerova, 1991; Panitch and Berg, 1970; Vandertop, Hoffman, Drake *et al.,* 1992) or an incidence rate as high as medulloblastoma and astrocytoma tumours (Stroink *et al.,* 1987). A low incidence rate of 5% to 20% is reported in a series of unbiopsied brain stem gliomas (Cohen & Duffner, 1984; Undjian *et al.,* 1989). The brain stem gliomas in the sample were confirmed by either a histology report, CT scan or MRI report. As the quality of imaging has improved over the last 10 years, allowing for earlier detection of lesions, a concomitant

variation in the incidence rate has emerged (Packer, Zimmerman, Luerssen *et al.,* 1985; Smith, 1990).

The 18% incidence of cerebellar astrocytoma tumours in the sample is low according to international studies, in which incidence rates of 25% to 35% are reported (Campbell & Stanley 1996; Packer *et al.,* 1990; Schneider Jr., Raffel & McComb, 1992). Although great care was taken to find all the files, one of the difficulties in a retrospective study remains the problem of lost information. All the files listed on the computer were found.

The 8% incidence rate of ependymoma tumours falls within the incidence rate of 5% to 10% reported by other international studies (Cohen & Duffner, 1984; Undjian *et al.,* 1989).

Of the 174 posterior fossa brain tumours identified, 44.3% of the subjects have survived and 43.7% are deceased, while 12% of cases are lost-to-follow-up. The study supports the overall 10 and 20 year survival rates of 44% and 37% reported respectively for irradiated paediatric brain tumours (Jenkin *et al.,* 1995). These survival rates are dependent on the diagnosis of the type of brain tumour and the treatment provided.

The pattern of tumours in the deceased group is similar to that found in other studies: 53% are brain stem gliomas, 31% are medulloblastomas, 8% are ependymomas and 7% are cerebellar astrocytoma tumours which has shown little change over the years (SEER, 1983-1987).

In the tested sample of 51 survivors of paediatric posterior fossa brain tumours, 59% of the tumours are medulloblastomas, 31% are astrocytomas, 8% are ependymomas and 2% are brain stem glioma tumours. The different types of posterior fossa tumour in the tested

sample is similar to that in international studies on neuropsychological and quality of life functioning (Duffner *et al.,* 1983; LeBaron *et al.,* 1988; Packer *et al.,* 1989; Sutton *et al.,* 1989). Medulloblastomas are the most common type of tumour (Halperin *et al.,* 1994).

Although no significant differences were found between the treatment groups in terms of SES, 31% of the sample had occupations distributed among the manual, unskilled and menial occupational categories.

SES is often not reported in international studies of survivors of brain tumours (Ris and Noll, 1994), so that the contribution of SES to the rehabilitation of the brain-damaged child remains unexplored. However, an attempt was made to counteract this possibility by including a Psychosocial Adversity Scale that was used by the Head Injury Research Group at Groote Schuur Hospital (Hemp, 1989). In terms of this the head injury children are a more disadvantaged group than the posterior fossa tumour survivors. In the latter group, there was little difference in the mean Psychosocial Adversity Rating Score between the treatment groups. Nonetheless, a general finding was that 41% of the mothers had less than standard 6 (grade 8) level of education, with the incidence increasing slightly from Group 1 to Group 3 (33% - 47%). Within the province of the Western Cape, the mean number of years of schooling of persons age 25 years and older is 8.45 years or a grade 8 level of education (October Household Survey in Central Statistics, 1996). Thirty nine percent of the parents are unemployed and reflect the present economic climate in which retrenchment and unemployment figures in the country are increasing (Nxumalo, 1999).

Thirty five percent of survivors come from single parent units. Thus, a third of the children may come from social units in which the mothers are both educationally disadvantaged and lack the skills necessary to stimulate brain-injured children. The concomitant high incidence of single parents, lack of occupational skills and unemployment adds to the burden of caring

for these children. The lack of resources available for the optimal development of the child and the dependence of children on their family to use the resources available to them are further difficulties. The children in this study probably have more Psychosocial Adversity in their backgrounds than survivors in other global studies.

13.2 TREATMENT RELATED OUTCOMES

The aim of the research was to explore differences in neuropsychological functioning and health-related quality of life in survivors of paediatric posterior fossa brain tumours. A retrospective research design over a 28 year time span, involving 51 subjects, grouped according to the three treatment parameters (Group 1 = surgery only; Group 2 = surgery and RT; Group 3 = surgery, RT and chemotherapy) was used (See Appendix A).

An overall finding is that children treated by means of surgery, RT and chemotherapy (Group 3) have the greatest incidence of problems, such as pretreatment negative factors and post-operative complications, in addition to the burden of treatment factors such as surgery, radiotherapy and chemotherapy which adversely affected their neuropsychological and quality of life functioning. It is difficult to extrapolate which of these factors are responsible for the low scores as the type of tumour which prescribes the treatment is implicated in the findings.

The survivors in treatment Group 3, the medulloblastoma subjects treated by means of surgery, radiotherapy and chemotherapy have the shortest mean duration of presenting symptoms compared with the children in treatment Group 1 treated by means of surgery only, for their astrocytoma tumours (9 weeks versus 11 weeks). This suggests that medulloblastoma tumours develop at a faster rate than astrocytoma tumours, as described by Halperin *et al.*, (1994). Moreover a shorter duration of presenting symptoms is associated with a poorer outcome (Packer *et al.*, 1987).

All the children in treatment Group 3 required some form of drainage procedure, either a ventriculo-peritoneal shunt or an external ventricular drain, to relieve signs of intracranial pressure prior to treatment. The incidence of such procedures was slightly lower for the other treatment groups (Group 1 = 83% and Group 2 =70%). According to Kumar *et al.,* (1996) children with posterior fossa tumours are predisposed to hydrocephalus because of the proximity of the fourth ventricle to the CNS pathways. Tumour site thus is an important variable in the consideration of the effects of ICP on outcome. Treatment Group 3 children presented with the highest percentage of signs of papilloedema and cerebellar motor disturbance followed by treatment Group 2. The children in treatment Group 1, the surgery only group had the lowest percentage. This may suggest a higher incidence of CNS impairment prior to treatment in Group 3 subjects treated by means of surgery, radiotherapy and chemotherapy, than the other treatment Groups as well as a more aggressive type of tumour.

The survivors of Group 3, all of whom had medulloblastoma tumours treated by means of surgery, radiotherapy and chemotherapy had the least number of cases (32%) which were amenable to total surgical resection. This indicates that the group may have had tumours which were invading critical areas where such surgery may have caused neurological damage as postulated by Halperin *et al.,* (1994). A high percentage (83%) of total surgical resections occurred in the surgery only treatment Group1, in which all the children had the astrocytoma tumours, compared with treatment Group 2 (45%), the children treated by means of surgery and radiotherapy for a variety of posterior fossa tumours. Tumour type and the associated natural morbidity of the tumour are therefore potentially confounding issues in the investigation of the effects of treatment on neuropsychological outcome.

Ris and Noll (1994) report that the findings on the relationship between the extent of surgical resection and neuropsychological outcome are

inconsistent. Although the study of Bordeaux *et al.,* (1988) is limited by a small sample, surgery itself was not shown to be associated with poor neuropsychological test scores. In this study there were no differences in prorated FSIQ scores (FSIQ = 79 versus 73) between the children who had undergone total surgical resection compared with those who had undergone subtotal surgical resections. This finding is similar to Ellenberg *et al., (*1987), Johnson *et al.,* (1994) and Yang *et al.,* (1997) but not supported by Packer *et al.,* (1987). A methodological consideration in the interpretation of the outcome is how the extent of the resection is described. In the present study, the extent of the surgical resection is defined by the neurosurgeons' operation notes. Packer *et al.,* (1987) report the extent of the surgical resection according to the impressions of the surgeon and the post-operative CT scan. They suggest that the extent of the surgical resection is significantly related to FSIQ scores. They also found that larger tumours (which cannot be resected) contributed to permanent CNS damage prior to diagnosis and also to peri-operative and post-operative mental state. The diverse manner in which the neurosurgical resection of the tumour is defined, as well as the pre-operative and post-operative management of the children are thus sources of variance which contribute to the neuropsychological outcome.

As most of the children in the sample had ventriculo-peritoneal shunts inserted prior to treatment, the treatment-related effects of a single shunt placement on FSIQ could not be adequately explored. According to the review by Ris and Noll (1994) the majority of research indicates that, if the effects of raised intracranial pressure are promptly treated by means of shunting, or surgical removal of the obstruction caused by the tumour, there will be no lasting measurable effects. The children who had repeated shunt revisions had statistically significant lower mean prorated FSIQ scores than those without such revisions (FSIQ =58 versus 81). Kao *et al.,* (1994) had a similar finding. Shunt revisions, as discussed by Scott (1991), are usually performed to relieve obstructions, wound complications, infections and other complications that occur subsequent

to shunting. In the present sample, shunt revisions occurred as a complication of shunt infections subsequent to shunting.

The subjects in Group 3, treated by means of surgery, radiotherapy and chemotherapy have the highest incidence of intra operative and post-treatment complications (53%), such as infection, transient cerebellar mutism and seizures compared with treatment Group 2 subjects (30%), treated by means of surgery and radiotherapy and treatment Group 1 subjects (25%) treated by means of surgery only. Growth hormone treatment complications, such as short stature and weight are also more prevalent in the children with medulloblastoma tumours treated with surgery, radiotherapy and chemotherapy than the children in treatment Group 1 with surgically resected astrocytoma tumours.

A comforting finding for the parents of children who experienced transient cerebellar mutism is that there is no difference in the prorated FSIQ scores between those who presented with mutism (FSIQ = 73) and those who did not (FSIQ=76). The 12% incidence of cerebellar mutism found in the sample, is marginally higher than that reported by Dailey *et al.,* (1995) and Pollack *et al.,* (1995). To date, no research in the literature on the effects of cerebellar mutism on FSIQ is described. An unexpected finding was a single case of visual impairment in association with cerebellar mutism, in which a good visual recovery paralleled the return to normal speech. Visual impairment associated with transient cerebellar mutism has since been described by Liu *et al.,* (1998) who investigate four cases, all of whom made an excellent recovery.

A low seizure incidence rate for children treated for posterior fossa tumours is reported by Cohen and Duffner (1984), Gjerris (1976), Hoppe-Hirsch *et al.,* (1990) and Syndikus *et al.,* (1994). Children presenting in this study who had post-operative seizures have lower mean prorated FSIQ scores (57) than those who did not have seizures (77), but only three children suffered such seizures. Of the three children one child had

an astrocytoma tumour and was treated by means of surgery only and the remaining two children had medulloblastoma tumours treated by means of surgery, radiotherapy and chemotherapy. Syndikus *et al.,* (1994) reported that epilepsy was the only independent variable associated with poor cognitive functioning.

The mean height of the Group 3 survivors, treated by means of surgery, radiotherapy and chemotherapy, is at the 23rd percentile which is significantly worse than that of the survivors in Group 1 (55th percentile), treated by means of surgery only and children in Group 2 (40th percentile), treated by means of surgery and radiotherapy. These results are similar to other research findings that indicate that, with the adjuncts of cranial RT and chemotherapy treatment, children grow less in terms of height (Brauner *et al.,* 1989; Chin & Maruyama, 1984; Duffner and Cohen, 1991; Hirsch *et al.,* 1979; Johnson *et al.,* 1994; Lam, Tse, Wang *et al.,* 1987; Moshang Jr. *et al.,* 1996; Moore *et al.,* 1992; Mulhern *et al.,* 1989; Nishiyama *et al.,* 1994; Onoyama *et al.,* 1975; Syndikus *et al.,* 1994).

The findings also imply that the combination of cranial and spinal irradiation treatment has negatively affected the height of the children in both treatment Group 3 and Group 2. According to Brauner *et al.,* (1989), most of the growth retardation may be due to the lack of spinal growth. They suggest that GH deficiency may only occur 12 to 24 months after cranial irradiation. The impact of cranial irradiation treatment on growth may be limited only to this period. The effect of Time-since-Treatment is therefore an unknown influence on these results. A recent finding by Robertson *et al.,* (1997) proposes that tumour type, that is astrocytoma versus medulloblastoma tumour, may influence the growth of subjects prior to treatment, irrespective of Age-at-Diagnosis. This result needs further clarification in future studies.

Although there is no statistically significant difference in weight between the treatment groups (Group 1 = 44th percentile; Group 2 = 36th percentile

and Group 3 = 26th percentile), there is a trend toward a decrease in weight. Weight gain or loss is seldom reported in studies. However when it is reported, few children treated with combinations of surgery, RT and chemotherapy show weight loss (Bamford *et al.,* 1976; Li *et al.,* 1984; Onoyama *et al.,* 1975).

Thus the survivors in treatment Group 3, had the shortest duration of presenting symptoms, the highest incidence of pretreatment symptoms of papilloedema and cerebellar signs, as well as the highest incidence of shunts or a drains inserted to relieve raised ICP. Treatment Group 3 subjects also had the least number of cases amenable to total surgical resections, as well as the highest incidence of post-operative complications, before receiving the additional treatments of RT and chemotherapy.

By comparison Group 1 cases treated by means of surgery only, had a similar duration of presenting symptoms as Group 2 subjects who had been treated by means of surgery and RT. However, Group 1 had a lower incidence of signs of papiloedema and cerebellar difficulties and a higher number of cases amenable to total surgical resections. They also had one child who presented with seizures whereas no children in treatment Group 2 presented with this disorder and less cases of post-operative complications such as infection and mutism than treatment Group 2 children. Of importance is that the children in Group 1, the surgery only group, had more cases with shunts inserted prior to treatment to relieve signs of raised ICP (83%) compared to the children in Group 2, treated by means of surgery and radiotherapy, who had shunts (65%) and a drain inserted (5%). The Group 1 children, treated by means of surgery only, thus presented with a higher incidence of RIP than those in treatment Group 2 and a concomitant higher incidence of shunts that were not removed. Over the years it has been the policy of the Department of Neurosurgery to relieve signs of RIP by the insertion of a shunt or a drain prior to surgery, this policy has since changed. Once a shunt is inserted it

is a permanent structure which is only removed if the child presents with shunt complications. None of the children in the surgery only treatment Group 1 had a shunt revision or removal. According to Raimondi and Tomita (1981) although the brain tumour itself causes signs of RIP, the complicating secondary hydrocephalus is often responsible for RIP. The child may thus be considered to have two distinctly different diseases the tumour and hydrocephalus which complicate one another and contribute to the complex picture of RIP. Hydrocephalus is a dynamic disorder and without confirmation on CT scan one is unable to ascertain if the ventricles have or have not returned to their normal size. The research findings on the neuropsychological effects of RIP and shunts in children with brain tumours are contradictory as the type of tumour, treatment variables, age at diagnosis of the children as well as the type of study are complicating factors. Low FSIQ scores are reported by some researchers (Jannoun & Bloom, 1990; Packer *et al.,* 1987) or higher FSIQ scores in those who had shunts compared to those who did not have shunts (Johnson *et al.,* 1994) whereas other researchers found no difference in FSIQ scores in children who had shunts to relive RIP (Ellenberg *et al.,* 1987; Yang *et al.,* 1997). Hydrocephalus as a disease entity has been extensively studied by many researchers (Dennis *et al.,* 1981; Dennis *et al.,* 1987; Fletcher *et al.,* 1992). With improvement in treatment modalities over the last thirty years the emphasis in the research has changed to adopting a developmental perspective that considers the nature of the cognitive deficit, it's characteristic over age and the relationship to the particular forms and manifestations of early onset hydrocephalus (Dennis, 1999). Hydrocephalus predisposes children to changes in white matter which have adverse consequences for neuropsychological function. Recent research by Mulhern *et al.,* (1999) has shown that children treated for medulloblastoma tumours have significantly less normal white matter and lower FSIQ scores than those treated for low grade cerbellar astrocytoma tumours thus lending support for the low FSIQ scores of the medulloblastoma subjects. However, the children in treatment Group 1 all of whom had low grade cerebellar astrocytoma tumours should therefore

not be predisposed to changes in cerebral white and subsequent low FSIQ scores as their treatment comprised of surgery only and not radiotherapy or chemotherapy which were found to be the reasons for the white matter changes. However, none of the children in Mulhern's study had shunts. Thus, without CT or MRI evidence, one is unsure of the consequence of permanent shunt placement on the developing brain of the children with cerebellar astrocytoma tumours in Group 1 treated by means of surgery only.

It is therefore apparent that subjects in treatment Group 1, the surgery only group, apart from having permanent shunts, have the lowest incidence of pre-treatment and post-treatment complications which should not adversely affect their neuropsychological outcome compared with treatment Group 2 subjects, the surgery and radiotherapy group, and treatment Group 3 subjects, the surgery, radiotherapy and chemotherapy group.

13.3. NEUROPSYCHOLOGICAL OUTCOMES

The differences between the treatment groups in several neuropsychological domains were explored. On at least one measure in the domains of attention, visual perceptual processing, memory and motor functioning, the Group 3 survivors, treated by means of surgery, radiotherapy and chemotherapy, had significantly lower scores.

13.3.1 Intelligence

No statistically significant differences were found in the prorated FSIQ, VIQ or PIQ test scores between the treatment groups. Inspection of the IQ test pattern in the treatment groups shows that the mean prorated FSIQ scores of both Group 1 (FSIQ=78) and Group 2 (FSIQ=81) are within the borderline range of intellectual functioning (according to DSM –IV). The mean prorated FSIQ score of Group 3 (FSIQ=70) is on the cusp of the DSM-1V mild mental retardation / borderline range.

All the groups have a wide range of prorated FSIQ scores (40-118). Similar findings are reported for survivors of medulloblastoma tumours treated with surgery, RT and/or chemotherapy. Of the researchers who report FSIQ scores, Hirsch *et al.,* (1979) found 31% of the sample had FSIQ < 70 and only 11% had FSIQ >90; Duffner *et al.,* (1983) showed that 50% had FSIQ <80; Johnson *et al.,* (1994) indicated that FSIQ scores ranged from moderately retarded to low average; Silverman *et al.,* (1984) found low average to average FSIQ scores while Yang *et al.,* (1997) reported mean below average FSIQ scores. In several studies, the effects on FSIQ of tumour site are not clear as the samples contain mixed supratentorial and infratentorial tumours. In addition those cases who received RT and those who received RT and chemotherapy are often not specified. In the present sample, the treatment combinations of surgery, RT and chemotherapy are clearly defined and the sample is a homogenous sample in terms of tumour site: all the tumours are posterior fossa tumours.

Examination of the details of the children in the mental retardation range suggests that complications following the treatment may have contributed to the low scores. In all three treatment groups, these children had seizures, shunt revisions or transient cerebellar mutism.

The differences between VIQ and PIQ in the treatment groups are not significant. This is consistent with Kun *et al.,* (1983); LeBaron *et al.,* (1988) and Silverman *et al.,* (1984) who recorded no discrepancy between VIQ and PIQ scores. However, other researchers have found VIQ to be significantly higher than PIQ (Dennis *et al.,* 1996; Johnson *et al.,* 1994; Mulhern and Kun, 1985; Moore *et al.,* 1992; Packer *et al.,* 1989; Sutton *et al.,* 1989).

The possibility that the different IQ tests used in this study may have contributed in some way to the IQ test scores has been considered. The

mean IQ test scores for the age-related IQ tests used are given in the Appendix G. The wide scatter of the scores on all the IQ tests indicate that the composition of the sample rather than the type of test used contributed to the findings. A review of the literature (Chapter 6 and Appendix H) shows that when more than one type of measure was used to assess cognition this was not discussed in the interpretation of the results (Brookshire *et al.,* 1990; Bordeaux *et al.,* 1983; Chadderton *et al.,* 1995; Dennis, Spiegler, Fitz *et al.,* 1991; Dennis Spiegler, Hoffman *et al.,* 1991; Dennis *et al.,* 1992; Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Grill *et al.,* 1999; Johnson *et al.,* 1994; LeBaron *et al.,* 1988; Moore *et al.,* 1992; Packer at al., 1989; Radcliffe *et al.,* 1992; Seaver *et al.,* 1994; Sutton *et al.,* 1989). However Silber *et al.,* (1992) made use of eight different IQ test instruments to measure intellectual and developmental functioning. They are of the opinion that the change to a different test instruments did not contribute significantly to the intellectual outcome.

In the South African context the SSAIS-R intelligence test as explained in Chapter 7 has norms for both advantaged and environmentally disadvantaged subjects. These norms were devised to correct for the deprived environmental factors and used on the children who used the test. The number of children in each treatment group tested on the SSAIS-R is consistent across the treatment groups (see Appendix G).

As no significant differences between the treatment groups was found in the sample as regards the demographic factors, occupation as a measure of socio economic status and psychosocial adversity, it was not considered necessary to adjust the FSIQ scores to take these factors into account. None the less given the 41% incidence of mothers who have less than standard six level of education in the sample, education is an important contributing factor to test performance. According to Nell (2000) formal schooling and urbanization override ethnicity as a contribution to test performance variance in culturally different settings and are also more important than traditional sources of variances found in age, sex and

socioeconomic factors. These factors may thus play some part in the wide scatter of the prorated FSIQ scores and possible reflect the diversity of the sample.

Age-at-Diagnosis for the entire sample had no significant effect on prorated FSIQ score. The effects (or lack of them) for Age-at-Diagnosis are discussed later in this chapter.

13.3.2 Attention

A statistically significant difference in performance in Digit Repetition scale scores showed that subjects in Group 3, treated by means of surgery, radiotherapy and chemotherapy, had an impaired performance compared with subjects in treatment Groups 1, surgery only group, and treatment Group 2, surgery and radiotherapy subjects, who had similar results. The effects of RT per se on tasks of attention are not clear. Dennis *et al.*, (1998) found that children treated with RT performed more poorly than those treated without RT on both focused and selective attention tasks. Moore, Copeland *et al.*, (1992). reported that the effects on survivors of different types of cancer, other than brain tumours, treated with cranial irradiation and chemotherapy indicated that they were slower on their mean reaction time compared with their sibling controls. As a variety of tests have been used to measure attention, researchers have found differing results.

In the present small sample of adult subjects, the scores of all the subjects were in the impaired range on TMT A (mean = 14th Percentile) but a slightly better performance was found on TMT B. (mean = 25th Percentile) These timed tests measure speed of attention, sequencing, mental flexibility, visual search and motor functions. TMT B is more difficult than Part A as the subject has to show the ability to do simultaneous mental tracking, that is, the ability to alternate between counting and the alphabet. The results thus indicate that performance of

the posterior fossa brain tumour subjects is more compromised by motor speed, attention and visual search than double mental tracking. Unfortunately the small number of subjects in the treatment groups restrict further interpretation. Dennis *et al.,* (1998) found that that the attention of subjects with posterior fossa tumours is likely to be compromised.Tumour or surgically-related disturbance of the reticular activating system could be a common mechanism for slow performance found on TMT A and B as proposed by Riva *et al.,* (1989).Moore, *et al.,* (1992) suggest that the slowing of cortical activity secondary to white matter damage, as a result of intensive CNS therapy, especially cranial irradiation, may account for the slow performance found on test scores, as shown on TMT A and TMT B.

13.3.3 Visual Perceptual Information Processing

Group 3 subjects treated by means of surgery, RT and chemotherapy had statistically lower results on Block Design, Coding and VMI (Beery) than the other groups. Visual motor integration, fine motor speed and dexterity difficulties were also found following treatment of posterior fossa tumours by means of surgery, RT and chemotherapy according to Hoppe-Hirsch *et al.,* (1995) Packer *et al.,* (1987), Packer *et al.,* (1989). Children with cancer other than brain tumours, treated with chemotherapy and RT but excluding surgery, have been found by Moore *et al.,* (1992) also to have impaired visual motor integration skills.

There were no differences between treatment Group 1, surgery only group and treatment Group 2, surgery and radiotherapy group, in terms of Coding. There was a trend for lower Block Design scores to be found in Group 2 than Group 1, but the difference between these two treatment groups reached statistical significance only for VMI (Beery), where Group 2 subjects, treated by means of surgery and radiotherapy, were clearly impaired (mean=19th percentile).

In the motor-free test of Visual Spatial Relations, the subjects in all the groups had impaired scores. However, this outcome was not obtained on the motor-free test of Visual Discrimination. There was a significant difference between the groups only when a motor function was added as in the Visual Motor Integration task of the Beery. Johnson *et al.,* (1994), in a group of medulloblastoma survivors treated with surgery and adjuvant therapy, also discovered that visual perceptual information processing difficulty became evident when motor function skills were required.

Age-at-Diagnosis did not significantly affect the scores on VMI as measured by the Beery. However, a statistically significant difference was found between Years-since-Treatment and the copying of the Beery designs. The longer the Years-since-Treatment, the poorer the scores on the VMI. In the present study the scores for the entire sample on the VMI (Beery) were impaired. The posterior fossa site of the tumour, as well as the treatment parameters of surgery only, surgery and RT, and surgery, RT and chemotherapy appears to be implicated in these results.

13.3.4 Memory Functions

A statistically significant difference between the treatment Groups was found in the non-motor test of Immediate Visual Memory Recall (TVPS). Group 3 had the most impaired performance (26th percentile) whereas Group 1 (51st percentile) and Group 2 (60th percentile) functioned in the average range. A possible motor confound is ruled out by the use of a non- motor test, but the problem may be in visual perceptual difficulties rather than visual memory. This is indicated by the impaired scores in the non- motor Visual Spatial Relations (TVPS) as well as the downward trend across the groups of the scores in Visual Discrimination (TVPS) in terms of treatment. Few researchers have explored visual memory parameters associated with treatment although Johnson *et al.,* (1994) found visual memory deficits associated with treatment by surgery and

adjuvant protocols for medulloblastoma tumours. Lazareff and Castro-Sierra (1996), on the other hand, reported no visual memory deficits in children with cerebellar tumours treated by means of surgery only, either at preoperative or post- operative testing.

Age-at-Diagnosis did not have a statistically significant effect on TVPS-visual memory but the scatterplot shows a slight improvement with increasing Age-at-Diagnosis, although all the scores are within the impaired range of functioning. Years-since-Treatment did not have a significant effect on TVPS visual memory performance but the scores for the entire sample were in the impaired range.

There is a statistically significant difference between the treatment Groups on the Auditory Verbal Learning Test (AVLT) total scores. The surgery, RT and chemotherapy group (Group 3) had the poorest performance with no clear trend indicated for Group 1, surgery only, or Group 2, surgery, radiotherapy and chemotherapy. Packer *et al.,* (1987) find that one third of the long-term survivors treated with surgery, RT and chemotherapy had deficits in verbal memory. Group 3 also had a poorer, although non-significant, performance on the Recognition Task.

Working memory involves the "active processing of incoming information and the prospective updating of the memory" (Dennis *et al.,* 1998, p27).

The response of the subjects in treatment Group 3 on the AVLT learning curve indicated that the children were slow to start (Trial 1), had difficulty in sustaining their attention after an interference task (Trial 6) and had difficulty in shifting their response from one task to another. In this manner they fulfilled the criteria for working memory difficulties.

All school going children under the age of 18 years, who were tested on the SSAIS-R for auditory verbal story memory, achieved scores in the average range regardless of treatment. Subjects older than 18 years who

were tested on the WMS-R story memory also had few differences in scores according to treatment. The scores of treatment Group 3 subjects were considerably lower than those of treatment Group 1 and treatment Group 2 both on (WMS-R) immediate and delayed recall. All the subjects were able to maintain their scores from immediate to delayed recall, indicating that the group as a whole had no difficulty in retrieving verbal information. The small number of participants in each treatment group and the uneven distribution of the subjects into treatment groups is a potential confound in the interpretation of the results.

Differences on the AVLT total scores according to Age-at-Diagnosis were not significant. Mulhern and Kun (1985), report that verbal memory difficulties are related to younger Age-at-Diagnosis.

The AVLT scores differed statistically significantly between the different Years-since-Treatment groups but no clear directional trend is evident. The lowest scores appear to be after seven to ten years post-treatment while the scores at ten Years-since-Treatment seem to be the highest scores. The use of raw scores may reflect the expected increase from childhood to adulthood. The impairment in memory functions is possibly sensitive to the time at which memory was assessed. Bordeaux *et al.*, (1988) recorded no significant changes in verbal memory in children tested within one year following treatment of radiotherapy, whereas Packer *et al.*, (1989) showed at two years post treatment, almost half the children treated by means of RT performed below the normal range, while 64% had difficulties in immediate auditory recall.

Subjects in Group 3, treated by means of surgery, RT and chemotherapy have the most impaired scores on working memory as well as on verbal learning, according to the scores on the AVLT.

13.3.5 Motor Functions

Schmahmann (1997) reports that impaired voluntary control motor functions are an expected finding in survivors of cerebellar brain tumours, due to their location in the posterior fossa. Both the site of the tumour and the different treatment protocols appear to be implicated in the difficulties in motor functioning.

Differences between the treatment groups were evident in the execution of the Purdue Pegboard on the preferred hand, non-preferred hand and both hands. On all three parameters, subjects in treatment Group 3 had a statistically significantly worse performance, with the scores of other treatment groups in the below average range. A similar outcome was indicated in the execution of Successive Finger Taps in which Group 3 subjects, treated by means of surgery, radiotherapy and chemotherapy had significantly slower scores than the other treatment groups. There was no clear trend between the performance of subjects in treatment Group 1, surgery only and treatment involving surgery and radiotherapy, Group 2 subjects. Impaired motor functions in survivors of posterior fossa tumours, treated with combinations of surgery and adjuvant therapy have been reported by other researchers (Brookshire *et al.*, 1990; Johnson *et al.,* 1994; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; LeBaron *et al.,* 1988; Packer *et al.,* 1989). Roux (1987) also found treatment related impairment in fine motor co-ordination in ALL children treated with chemotherapy and RT.

Ataxic gait was not significantly different between the treatment Groups although subjects in Group 3, treated by means of surgery, radiotherapy and chemotherapy showed a significant impairment in the ability to balance on both the preferred and the non-preferred leg. A similar finding with regard to balance is reported by Lannering *et al.,* (1990).

Age-at-Diagnosis and Years-since-Treatment had little impact on the Purdue Pegboard (using both hands) scores.

13.3.6 Formulation Of Findings Pertaining To Treatment

In summary, Group 3 survivors treated by means of surgery RT and chemotherapy had the worst outcome in the domains of attention, visual motor integration, visual memory, verbal learning and fine motor dexterity. The differences between Group 1, surgery only, and Group 2, surgery and radiotherapy, were not found to be statistically significant except on the VMI (Beery) in which subjects in treatment Group 1 performed statistically significantly better than those in treatment Group 2. In addition on the Blocks, the trend was for Group 1 surgery only subjects, to have a slightly better performance than Group 2, surgery and radiotherapy subjects. There was also a trend for Group 2 subjects to have slightly better score than Group 1 subjects on the verbal tests of Comprehension and Similarities, as well as the non-motor Visual Memory test.

It is therefore evident that the neuropsychological battery of tests highlights the differences between the treatment groups in the domains of functioning. However, the differences between the treatment Groups cannot be attributed solely to the various combinations of the treatment of surgery and adjuvant chemotherapy. The Group 1 subjects who had the astrocytoma low grade tumours treated by means of surgery only, should possibly have perform better than the other Groups treated by means of combinations of surgery, RT and chemotherapy. This has only been statistically confirmed on the VMI (Beery) with a trend shown on Blocks.
As discussed the insertion of a pretreatment shunt in the majority of the children in surgery only treatment Group 1 may be contributing to the lower than expected cognitive test scores of the group.

The type of posterior fossa tumour is also implicated as shown by the finding that the scores of the children with low grade astrocytoma tumours in Group 1 were only significantly better than those of both treatment Groups 2 and Group 3 on the VMI (Beery). Both these treatment groups have a variety of posterior fossa tumours, with a predominance of

medulloblastoma tumours treated with various combinations of radiotherapy and chemotherapy. Thus, although tumour type is implicated, it is difficult to determine if it is the type of tumour alone or the combination of the type of tumour and the treatment which is causing the difference in test scores.

A consistent finding is that Group 3, survivors treated with surgery RT and chemotherapy had the worst scores. However, this group also had the highest incidence of adverse pretreatment factors, as well the least number of cases amenable to total surgical resections and the highest incidence of post-operative complications.

13.4. AGE-AT-DIAGNOSIS and YEARS-SINCE-TREATMENT

In an attempt to clarify the age-related factors, Age-at-Diagnosis and Years-since-Treatment were separately analysed on the test measures that were shown to be the most sensitive.

There were no significant effects for Age-at-Diagnosis on prorated FSIQ, AVLT-total score, VMI (Beery) and Pudue Pegboard. There appeared to be a difference between the Age-at-Diagnosis groups on the non-motor test of visual memory (TVPS), but this fell short of statistical significance. Inspection of the scattergram indicated a slight improvement in score with increasing Age-at-Diagnosis. The majority of research only explores the Age-at-Diagnosis effects on FSIQ scores and not those of other outcome variables as attempted in this study.

In other studies younger Age-at-Diagnosis has been found to be a critical variable as it is possible that those children treated earlier in their development are at greatest risk (Crossen *et al.,* 1994; Dennis *et al.,* 1996; Glauser & Packer, 1991; Roman & Sperduto, 1995; Ris & Noll, 1994). In this study differences between the three age groups were not significant, but on prorated FSIQ and Visual memory (TVPS) there was a

trend for those diagnosed after the age of seven years to have higher scores. Similar findings that neuropsychological functions were relatively unaffected if the diagnosis was made at the age of nine to ten years have been reported by Moore *et al.,* (1992), Sutton *et al.,* (1989), while Chin and Murayama (1984) cite children older than the age of eight at diagnosis.

Inspection of the individual Age-at-Diagnosis prorated FSIQ scores of the six children diagnosed at the age less than three years as cited by Packer (1999) to be a critical age, shows that the mean prorated FSIQ = 74.8, and ranged from 45-118. The wide scatter of the scores, the different treatment factors as well as the different tumour types are confounding factors in the interpretation of the results.

Mulhern *et al.,*(1999) reported that the rapidly proliferating brain cells are more vulnerable to the deleterious effects of CRT in children receiving CRT for medulloblastoma tumours with or without chemotherapy before the age of four years at treatment. Inspection of the individual prorated FSIQ scores of the children treated for medulloblastoma tumours showed that four children or 36% of the medulloblastoma group treated before the age of four years with S+RT, the mean prorated FSIQ scores = 87.5, compared to mean prorated FSIQ = 86.2 of the entire group. Thus little difference is indicated in scores. In the six children less than four years at diagnosis or 32% of the subjects in the medulloblatoma group treated by means of S+RT+C, the prorated FSIQ = 61.6 compared to prorated FSIQ = 69.8 of the group. Thus in the present sample of medulloblastoma subjects, age younger than four years at diagnosis does not appear to have any demonstrable impact on prorated FSIQ scores.

There was a statistically significant difference between the Years-since-Treatment groups on VMI (Beery) and the AVLT Total scores but not on prorated FSIQ, TVPS visual memory or Pudue Pegboard. The VMI (Beery) scores declined with Years-since-Treatment. This is clearly

illustrated on the scatterplot. However, there was no direction to the AVLT scores which were additionally considered to be confounded by using raw scores vulnerable to Age-at-Testing effects, and the small uneven distribution of subjects within each cell.

Interaction effects of Age-at-Diagnosis and Years-since-Treatment were further explored in a series of multiple regression analyses similar to those used in the Dennis *et al.,* (1996) study. Multiple regression analyses on the prorated IQ scores of the survivors of medulloblastoma tumours showed non-significant results for Age-at-Diagnosis and Years-since-Treatment. These were similar to the previous results of the entire sample in which Age-at-Diagnosis and Years-since-Treatment showed no significant effect on FSIQ scores.

When the medulloblastoma tumour sample was restricted to children less 18 years of Age-at-Testing, similar to Dennis *et al.,* (1996), multiple regression analyses showed a statistically predictive relationship between Time-since-Treatment and prorated FSIQ and VIQ. The longer the Time-since-Treatment the lower were FSIQ and VIQ, scores but not the PIQ scores.

This finding is similar to Dennis *et al.,* (1996), who discovered in a sample of children with medulloblastoma tumours treated with combinations of surgery, RT and chemotherapy, that the effect of Age-at-Diagnosis and Time-since-Treatment made separate contributions to IQ scores. In their model, VIQ declined with Time-since-Treatment and PIQ was relatively constant once established but varied with the Age-at-Diagnosis of the child.

In this research, a lower VIQ over Years-since-Treatment suggests that over the years the children have not developed age-appropriate verbal recovery abilities as suggested by Dennis *et al.,* (1996). This finding was only evident in the younger sample (those under 18 years at testing) and

not in the sample as a whole. Similar findings for children treated with surgery and adjuvant chemotherapy with posterior fossa tumours were indicated in the prospective study by Radcliffe *et al.,* (1992), in which there was a significant decline in VIQ from baseline to two years and thereafter VIQ seemed to stabilize at four years post diagnosis. This was not evident for PIQ. Sutton *et al.,* (1989) reported a significant decline in both VIQ and PIQ in medulloblastoma children tested over a two year period, whereas Packer *et al.,* (1989) found a non-significant decline in VIQ from baseline to year two post treatment and a marginally significant decline in PIQ.

Unfortunately, there are few prospective studies available on children with brain tumours who are followed up over a longer period of time to clarify the variable findings. The Japanese retrospective case report by Nishiyama *et al.,* (1994) of a monozygotic set of twins, one of whom was treated for a medulloblastoma brain tumour, shows that over a six year period the medulloblastoma twin had significantly lower scores on all IQ quotients than her twin. However, both twins had lower PIQ scores than VIQ scores.

The analyses for the time variables were repeated for the children in the astrocytoma group who had been treated by means of surgery only (Group 1 subjects with astrocytoma tumours). A multiple regression using Age-at-Diagnosis and Time-since-Treatment failed to produce any predictive relationships with the dependent IQ measures. The small sample unfortunately limits the results.

The retrospective nature of the design allowed for the composition of the treatment groups in terms of Years-since-Treatment, to be significantly different. Sheline in Crossen *et al.,* (1994) report that the sequential stages of RT reaction and the injury sustained in the brain observed on CT scan vary from necrosis to radiation encephalopathy and finally to atrophy. The end stage of radiation necrosis involves coagulation necrosis

and gross demeylination of the white matter in affected areas. Necrosis results from high doses of RT and generally may not manifest until nine to twelve months following treatment or even years later. Furthermore a functional compromise of the patient's neuropsychological status may occur without overt necrosis. The survivors in the sample were at both early and late stages of this process and the effects on neuropsychological scores are variable as shown in the analysis of the time results.

The inclusion of four subjects within six months after treatment spread across the treatment groups (Group 2 = 2 cases; Group 3 = 2 cases) is a debatable issue as regards the emergence of cognitive fall outs. Many studies have included children at both acute and later stages after treatment (Danoff *et al.,* 1982; Dennis *et al.,* 1996; Koa *et al.,* 1994; Lazereff *et al.,* 1996; LeBaron *et al.,* 1988; Yang *et al.,* 1997). Mulhern *et al.,*, (1985) investigated the acute effects of treatment on intellectual functioning and found that the younger age group showed a greater tendency to intellectual deterioration, whereas Bordeaux (1988) found that deficits observed at baseline testing were likely to be related to the effects of the tumour and not the treatment. A problem encountered by many researchers as well as the six longitudinal studies reviewed (Duffner *et al.,* 1988; Ellenberg *et al.,* 1987; Gajjar *et al.,*, 1994; Koa *et al.,* 1994; Mulhern *et al.,* 1989; Radcliff *et al.,* 1992) is the inclusion of a sufficient number of children across a broad range of ages to verify conclusive results. In the present study children across a broad range of ages were included in the study. However there were no infants under the age of one year in the study and the study was limited by the small number of subjects.

Future studies should correlate CT scan reports with neuropsychological testing as a means of clarifying the time effects.

13.5. TUMOUR TYPE

When the subjects were compared according to treatment, the low grade astrocytoma tumour subjects treated by means of surgery only, performed significantly better on Visual Motor Integration as measured by the Beery (VMI) than the subjects in the other treatment groups who had medulloblastoma, brain stem glioma and ependymoma brain tumours. Packer *et al.,* (1989) found that both astrocytoma and medulloblastoma groups had difficulty in visual motor integration and visual spatial difficulties after treatment, lending support to the idea of the functional role of the cerebellum in visual motor integration. The implication being that the type of tumour, (astrocytoma versus medulloblastoma), does not influence the neuropsychological outcome but that the difficulties are due to the treatment. Further support for the treatment, tumour debate has recently been shown by Mulhern at al., (1999). They showed that changes in qMRI and neuropsychological function are related to treatment with irradiation and chemotherapy as opposed to the site or type of tumour (astrocytoma versus medulloblastoma) and tumour surgery.

The Chadderton *et al.,* (1995) study on survivors of astrocytoma tumours in different areas of the brain, including the cerebellum showed that tumour site and site of treatment effect FSIQ scores. They reported that there was no difference at baseline testing in FSIQ scores in all subjects with low grade astrocytoma tumours located in different brain areas. The cranial irradiation recipients as well as those with cerebellar tumours performed significantly worse on all tests than those who were not treated with RT. However a small group of cerebellar astrocytoma survivors was treated with surgery and local field irradiation only to the posterior fossa area. This group had significantly lower FSIQ, VIQ and PIQ scores than the cerebellar tumours survivors treated by means of surgery only. On the basis of this finding, the authors hypothesized that this may be associated with disruption of the neural system involving subcortical structures and the frontal lobe. Daum and Ackerman (in Schmahnann 1997) explain that cerebellar patients have problems in shifting attention between modalities and this is presumed to be consistent with impaired cerebellar-frontal

interactions which modulate the ability to change attentional behaviour. The Chapman findings are interesting, but need to be investigated more fully with tests specific to frontal lobe function.

The relationship between RT dose and neuropsychological outcome may have shed more light on the role of treatment and tumour type. However as also found by Packer *et al.,* (1987) most of the children in the study received similar doses of RT. In addition the retrospective nature of the design and the concomitant changes in treatment over the 28 year period made it difficult to determine the contributions of the different treatment effects. Similar problems have been experienced by other researchers (Bordeaux *et al.,* 1988; Chin and Maruyama, 1984; Johnson *et al.,* 1994; Kao *et al.,* 1994; Sutton *et al.,* 1989).

In order to further explore the effects of treatment versus tumour type, a post hoc analysis was done of the children with medulloblastoma tumours. Groups 3 (Surgery+RT+ C) remained as before, while Group 4 was created from medulloblastoma tumours in Group 2 who had been treated with Surgery and RT only. At the commencement of this study no attempt was made to grade or classify the children with medulloblastoma tumours into "average risk" medulloblastoma or "poor risk" medulloblastoma as discussed by Packer (1999). This stratification was useful in the 1970's and early 1980's when "average risk" medulloblastoma tumours were treated with surgery and radiation and "poor risk" subjects treated with the addition of chemotherapy.

Over the years there has been a reassessment of the risk factors. Inspection of the treatment protocols in Appendix A indicates that none of medulloblastoma tumours in Group 4 have spinal metastases whereas Group 3 has one case of metastases and another of seedling deposits. In addition there is significant difference in the number of medulloblastoma tumours amenable to total surgical resections. Group 3 subjects treated by S+RT+C have a significantly higher incidence of sub total resections. Inspection of the Age-at-Diagnosis records shows that there is little

difference in the composition of the groups according to the stratification criteria of age less than three years old at diagnosis (Group 4 = 2 cases; Group 3 = 3 cases). Thus prior to adjuvant treatment or treatment by RT only, Group 3 subjects (S+RT+C) could possibly be assessed as "poor risk" children compared to Group 4 (S+RT) as "average risk".

Although the majority of children with medulloblastoma tumours needed a shunt or an EVD prior to surgery, three children treated by means of S+RT did not need a shunt or a drain compared to none in the S+RT+C treatment group. This suggests that children in Group 4 had a lower incidence of clinical signs of hydrocephalus than those in Group 3. The small numbers preclude further interpretation.

A statistically significant difference in prorated FSIQ scores was found between the medulloblastoma subjects treated by means of surgery and radiotherapy (prorated FSIQ in the low average range) and those treated by means of surgery, radiotherapy and chemotherapy (prorated FSIQ on the cusp of borderline / mental retardation range). Socio economic status was not found to significantly influence the prorated FSIQ scores, given the effects of the treatment variables. It is difficult to determine if the difference in scores is due to the treatment of radiotherapy and chemotherapy or the progression of the tumour prior to treatment. This finding lends support to Grill *et al.*, (1999) who reported that "poor risk" medulloblastoma subjects, such as those in the present sample, treated with surgery, radiotherapy and chemotherapy had lower FSIQ scores than children with "standard risk" medulloblastoma tumours. Few researchers take these factors into account.

Thus in the sample of medulloblastoma subjects those in Group 4 treated by means of S+RT are functioning better in terms of cognitive outcome than the subjects in medulloblastoma tumour Group 3 treated with surgery and radiotherapy and chemotherapy. A major gap in the understanding of the management of the children with medulloblastoma tumours is the lack

of biological factors which can be used to stratify the patients. The longitudinal study of Radcliffe *et al.,* (1992) showed that neither the progression of the tumour nor the site of the medulloblastoma tumour affected the FSIQ scores. This is possibly due to the biological nature of the tumour and the concomitant treatment of surgery, radiotherapy and chemotherapy. However the parameters associated with the effects of Age-at-Diagnosis, Age-at-Testing and Time-since-Treatment need further exploration in prospective cognitive and quality of life studies in which children are followed up for longer periods of time.

13.6. ROLE OF THE CEREBELLUM IN RELATION TO NEURO-PSYCHOLOGICAL FINDINGS

The majority of survivors in the study, regardless of type of tumour or treatment, had impairment of fine motor skills as indicated by the results obtained on the Purdue Pegboard. The cerebellar site of the tumour might have led one to expect difficulties in gait and balance, but in fact these were not found as a general effect. When difficulties were shown, these were attributed to adjuvant treatment as there was a trend for the scores to decrease from treatment Group 1 to treatment Group 3. Thus, variations in the ability to execute voluntary motor movements was shown in the sample and support the discussion of Daum and Ackerman in Schmahmann (1997). In their review of subjects with cerebellar malformations they state that cerebellar aplasia was frequently but not invariably associated with mental retardation. These authors report that the clinical symptoms related to malformations of the vermis or the cerebellar hemispheres showed considerable variability. In some cases there was no evidence of motor or intellectual impairment in life and the cerebellar malformations were accidentally discovered during post mortems. Therefore neither partial cerebellar malformations nor surgical removal of part of the cerebellum necessarily lead to clinically significant cognitive impairment. It is possible that impaired cognitive ability in

cerebellar developmental malformations may partly result from the impaired acquisition of psychomotor skills and it is difficult to disentangle the motor and non-motor consequences of early cerebellar dysfunction.

In terms of visual discrimination alone the groups seem unimpaired, but once visuomotor integration is required there is a downward trend according to treatment (Group 1 = 41st percentile, Group 2 = 19th percentile, Group 3 = 9th percentile). This suggests that it is the addition of a motor component that produces the effect.

According to Daum and Ackerman (1997), neuroimaging studies have helped clarify the role of the cerebellum in motor skill learning, such as the tracing of geometric patterns and the execution of serial movements. At the same time there is conflicting evidence with regard to visual spatial abilities in patients with cerebellar lesions.

The two-way link between the cerebellum and the parietal cortex has formed the theoretical base for the hypothesis of cerebellar involvement in visual spatial organization (Daum and Ackerman in Schmahmann, 1997). Studies supporting this hypothesis are the result of research on patients with cerebellar syndromes who have impaired visual spatial recall (Bracke-Tolkmitt, Linden, Canavan *et al.,* 1989 in Schmahmann, 1997) and impaired visual spatial manupulations (Wallesch and Horn 1990 in Schmahmann, 1997). Deficits in similar subjects have not been confirmed by other researchers (Appollonio, Grafman, Schwartz *et al.,* 1993; Daum, Ackermann, Schugens *et al.,* 1993a in Schmahmann 1997).

It is thus hypothesized that the cerebellum is involved in visual spatial organization. This is because disruptions of the cerebellar parietal pathway, due to tumours residing in the cerebellar vermis, and the treatment of the tumours, are associated with poor scores on the motor-free test visual spatial relations (TVPS) as well as visual motor integration (VMI). In addition impaired visual spatial recall is evident in

medulloblastoma survivors after adjuvant RT and chemotherapy treatment.

13.7. QUALITY OF LIFE OUTCOMES

13.7.1 WPBIC

Conspicuously absent from the literature on survivors of childhood brain tumours are the emotional and behavioural implications of the disease. The Walker Problem Behaviour Checklist (WPBIC) showed a negative correlation between problem behaviour and prorated FSIQ scores, which indicates that the lower the FSIQ, the higher the incidence of problem behaviours. Other research findings have not correlated problem behaviour with intellectual functioning in childhood tumour survivors.

The influence of treatment on problem behaviour was not significant. T scores above 60 on the WPBIC indicate problem behaviour. The trend of the total scores indicated that treatment Group 1 and treatment Group 2 subjects were functioning in the average range. Treatment Group 3 subjects (T=66) were functioning in the impaired range in problem behaviour. In terms of domains of behaviour, the group as a whole has problems in Acting Out behaviour. All the children in Group 3 treated with surgery, radiotherapy and chemotherapy, the majority of children in Group 1 treated with surgery only, but none on Group 2 treated with surgery and radiotherapy experienced some problems in Immaturity. More than half the children in Groups 2 and 3 have disturbed Peer Relations.

Research findings are inconsistent although an overall finding is that a high proportion of children treated for brain tumours may have chronic problems with emotional adjustment (Kun *et al.,* 1983; Lannering *et al.,* 1990; Mulhern and Kun, 1985; LeBaron *et al.,* 1988). Seaver *et al.,* (1994), however, found no difference between survivors of brain tumours and controls while Hoppe-Hirsch et *al.,* (1995) reported an increase in behaviour problems dependent on tumour type and treatment over a

period of time. According to Bauld *et al.,* (1998) no single predictor of psychosocial outcome has been identified in the adjustment of cancer survivors. A complex interaction of factors seems to play a role in the adjustment of cancer survivors making it difficult to establish which children are at greatest risk for psychosocial problems. Noll, Gartstein, Vannatta, *et al.,* (1999) support the finding that children with cancer receiving chemotherapy show considerable psychological hardiness. Most children in this study had scores within the normal range.

13.7.2 Health- Related Quality of Life

The Multiattribute Health Status Classification has six domains of functioning: sensation, mobility, emotion, cognition, self care and pain. Each domain has an attribute level which increases according to the degree of difficulty. A score is derived for each domain of functioning and a total score is also calculated.

Of the subjects, 64% have some degree of functional morbidity. The cognition, emotion and mobility domains were the most frequently endorsed areas of difficulty, as was also found by Whitton *et al.,* (1997) in adult brain tumour patients. Studies using the same rating scale on both children and adult brain tumour as well as ALL survivors, present varying results (Barr *et al.,* 1993; Bilson and Walker, 1994; Feeney *et al.,* 1993).

An exploration of the effects of treatment on health functioning showed no significant difference between the groups on the MHSC total score. However, there is trend for the total score to increase as the treatment parameters become more intense, from Group 1, surgery only to Group 3, surgery, radiotherapy and chemotherapy, which is similar to the finding by Barr *et al.,* (1993).

Significant negative correlations were found between the total score of the Multiattribute Health Status Classification (MHSC) and FSIQ, TVPS visual

memory, AVLT total score, VMI (Beery) and Purdue Pegboard using both hands. This implies that as the functional disabilities of the brain tumour survivors increase, the neuropsychological test score results are adversely affected.

A positive correlation was shown between Age-at-Diagnosis and emotion and pain as measured by MHSC in the treatment Group 3 subjects. This implies that the older the Age-at-Diagnosis, the higher the incidence of occasional emotional disturbance and pain in those having the more intense type of treatment. This finding is understandable bearing in mind that older children are more aware of the implications of the tumour and the treatment and of their differences from other children. Barr *et al.*, (1993) found emotional difficulties in younger age group survivors of ALL (mean age of four years eight months at-diagnosis) and associates greater radiation dose with emotional morbidity. The differences in findings may possible be because the Barr study is a prospective one in which the check list was completed by a panel of professionals who were familiar with the subjects, whereas this study is a retrospective design in which the checklist was completed by the parents and the survivors.

A significant correlation between Years-since-Treatment and sensation, as measured by MHSC, indicates that the longer the Years-since-Treatment (six years and more post treatment), the higher the incidence of subjects who need equipment for their sensory problem. A difficulty in seeing and hearing has been indicated by Whitton *et al.*, (1997). However, 71% of the subjects in the present study have not reported deficits in the domain of sensation. Similar findings are reported by Feeney *et al.*, (1993; 1992).

The MHRS offers a comprehensive, quick method of monitoring the functional health status of both adults and children. The domains of sensation, emotion and mobility are not broad enough in the scale used in

this study but these have been extended in the revised Health Utilities Index published Whitton *et al.*, (1997)

13.7.3 Educational Achievement and Occupational Status

More than 50% of the survivors in treatment Groups 1, surgery only and treatment Group 2, surgery, radiotherapy and chemotherapy were in normal school, in contrast to Group 3, surgery, radiotherapy and chemotherapy survivors, in which only 21% of the children were in normal school. Similar results have been shown by other researchers (Chadderton *et al.,* 1995; Duffner *et al.,* 1988; Hirsch *et al.,* 1979; Hoppe-Hirsch *et al.,* 1990; Hoppe-Hirsch *et al.,* 1995; Packer *et al.,* 1989; Yang *et al.,* 1997).

Kimmings *et al.,* (1995) found that the differences in academic potential can be related to the age of the child at diagnosis and the presence or absence of post operative complications. As less than half the group in the present study are aged 17 years or older (n=20) and treatment Group 1, surgery only, is composed of fewer subjects eligible for work (n=2), it is difficult to compare the effects of treatment on occupational outcome. Nonetheless of those eligible to work, nine adults (45%) are employed whereas five adults (25%) are at home and receive a disability grant. These recipients all experienced complications such as repeated shunt revisions, transient cerebellar mutism or seizures.

Lannering *et al.,* (1990) with a large sample reveal a higher percent to be employed (66%). According to Jannoun and Bloom (1990), 60% of brain tumour survivors were functioning in the average range of intelligence. Of this group 57% were leading normal lives without any neurological or physical difficulties. Hoppe-Hirsch *et al.,* (1990) with a longer follow up of medulloblastoma survivors presents a less positive picture. Ten years after the onset of the disease, no survivor had normal employment,

36% were unemployed and 64% worked in a protective workshop.

Research findings are thus varied and treatment factors, as well as treatment complications, may influence the occupational potential of brain tumour survivors. In addition, other factors such as SES, premorbid factors and rehabilitation opportunities may also influence the occupation potential of survivors.

13.8. PREDICTORS OF OUTCOME

Two Principal Components (PC1 and PC2) were identified from outcome variables which had been found to be sensitive to differences between the treatment groups: visual memory (TVPS), AVLT total score–verbal memory, VMI (Beery), Purdue Pegboard (both hands) plus prorated FSIQ.

PC1 appeared to comprise a global factor of intelligence and memory as it included FSIQ, TVPS visual memory and AVLT verbal memory and these accounted for 56% of the variance. PC1 was best predicted by a regression equation using SES, Repeated Shunt Revision, Tumour Type and Years-since-Treatment. Low SES, Repeated Shunt Revision and Medulloblastoma were negatively associated with PC1, whereas an increasing number of Years-since-Treatment was associated with better scores on PC1. It could be anticipated that low SES, Repeated Shunt Revisions and Medulloblastoma rather than Astrocytoma would be associated with a lower score on PC1, which is a global factor.

The association of increasing Years-since-Treatment with high scores on PC1 seems surprising considering the earlier finding that VIQ (which contributed to FSIQ in PC1) was negatively associated with Years-since-Treatment. However, it should be realized that this was for a smaller group comprising those under 18 years of age-at-testing and only subjects

with medulloblastomas. In addition PC1 comprises a memory factor as well as FSIQ.

PC2 which accounted for only 21% of the variance in the outcome variables used, comprised VMI (Beery) and Purdue Pegboard (both hands). PC2 seemed therefore to be a specific visual motor factor and was predicted by only Years-since-Treatment. An increasing number of Years-since-Treatment was associated with lower PC2 scores.

When tumour type and SES were used as predictors of PC2, only Tumour Type was significant, medulloblastoma being associated with poor scores. Medulloblastoma tumours appear to be more disruptive to visuomotor functions than astrocytomas, as children with medulloblastomas have had more posterior fossa irradiation than children with astrocytomas. This finding is therefore understandable.

In view of the retrospective nature of the study, the broad range of ages and the wide scatter of test scores, it seems unlikely that this model would be used to predict outcome from posterior fossa tumours. Nevertheless the model highlights the factors associated with good and bad cognitive and visuomotor outcome.

13.9. CONCLUSIONS

The following conclusions were drawn:

- The Quality of Life of children treated for posterior fossa tumours is influenced by a complex interrelationship of factors.

- Overall, children with posterior fossa tumours tended to have lower scores than the norm in the areas of intelligence, attention, visual perceptual information processing and motor functions. Relatively spared were speech and language functions. Although no distinct

neuropsychological profile is reported for children treated for brain tumours, the pattern of obtained scores is similar to that found by Fletcher and Copeland (1988) in children treated for ALL with prophylactic chemotherapy and cranial radiation.

- The survivors in Group 3, whose medulloblastoma tumours were treated by means of surgery, RT and chemotherapy, had impaired scores relative to the other treatment Groups in the domains of attention, visual perceptual information processing, visual memory, verbal list learning and motor functions.

- When the sample was restricted to only medulloblatoma survivors, those treated by means of S+RT performed significantly better than those treated by means of S+RT+C when measured on prorated FSIQ scores. This is possibly due to the biological nature of the tumour, which could not be verified due to the retrospective nature of the designs and the adjuvant treatment of chemotherapy. In addition one is unable to ascertain if the low scores of the S+RT+C survivors is due to the addition of chemotherapy, the two modalities given in combination or the relatively higher doses and volume of RT.

- In general quality of life (as measured by behaviour and health scales) was fair with Acting Out and Immaturity appearing as problems in school-age children. The majority of the survivors rated themselves, or were rated by their parents, as having an adequate functional level in the domains of sensation, mobility, emotion, cognition, self care and pain on the MHSC. About half the survivors were rated as having some degree of impairment on cognition, emotion and mobility. There were no significant differences between the treatment groups in terms of their behaviour ratings as shown on the WPBIC or health related functional status on the MHSC.

- Almost half the children attended normal school with more children from Group 3 treated by means of surgery, RT and chemotherapy

- attending special school or special classes compared to the other groups. Of the small number of survivors eligible to enter the work market, about half were employed.

- Age-at-Diagnosis did not have a significant effect on neuropsychological, behavioural or health-related outcome. Years-since-Treatment also failed to show a significant effect on behaviour and health scores and most of the neuropsychological scores, except that performance on the visual motor integration as measured by the Beery declined with increasing number of years. In analysing a smaller sample of subjects with medulloblastoma tumours, aged under 18 years at testing, VIQ and FSIQ showed a significant decline as a function of Years-since-Treatment, but PIQ was not affected.

- Complications such as repeated shunt revisions and seizures (the latter not significant due to small numbers) were associated with a lower FSIQ. Growth retardation was significantly greater in children undergoing RT and chemotherapy than in those having RT alone or those being treated with surgery only. A similar effect on weight was not found.

- Although it is known that the cerebellum is concerned with motor functions, it is hypothesized that the cerebellum is also involved in visual spatial organization.

- The Quality of Life of children being treated for posterior fossa brain tumours is thus compromised by the dilemma of the treatment prescribed to cure the disease. It is hoped, that although neither the incidence nor the adverse consequences of the treatment can be controlled, the neuropsychologist can directly improve the quality of

life of the children by advising and devising special educational programmes which build on the children' s capacity to learn and cope with the demands of daily living

13.10. LIMITATIONS OF STUDY AND RECOMMENDATIONS

One of the major methodological problems in making comparisons between the groups is that the unrestricted use of these comparisons can lead to a high probability of a Type 1 error. That is, the error of rejecting the null hypothesis when it is true (Howell, 1995). Another serious problem is a Type 11 error (the probability of not finding a difference between the Groups, that is there). According to Howell, the more positive approach is to discuss this in terms of power, which is the probability of correctly rejecting a false null hypothesis. In order to do this, four underlying assumptions have to be met, one of which is the size of the sample. As this study has a small number of subjects, it follows that only large effect sizes are reliably detected, while small and moderate effects remain unnoticed.

Another limitation to this study has been the retrospective nature of the design, bearing in mind the concomitant small number of patients, the uneven distribution of the test scores within the groups, the self selection of patients into treatment groups, the age cohort effect and the attrition of patient information. Future research should be a prospective longitudinal design, linked to international research centres in which a large patient population would meet uniform criteria and permit control of the possible confounding variables.

With the increased survival rate after treatment for brain tumours, the role of diet and stress in maintaining an adequate immune system is important. Future studies should take these factors into account.

Ris and Noll (1994) recommend smaller research centres such as training institutions which provide an opportunity to carry out prospective time restricted research studies on the development of neurobehavioural morbidity as it relates to specific neuro-anatomical structures and neuropathological processes. Such research could be linked to larger cooperative groups, combining the advantages of group and individual centres. In this way, by conducting investigations on homogenous groups of subjects who are receiving standardized treatment, more sophisticated types of research can be carried out.

A correlation between the CT scan findings and neuropsychological test scores may have clarified the treatment effects and age and time variables. This unfortunately was not possible but future studies should use imaging in conjunction with neuropsychological findings.

Children with brain tumours should be monitored with proton MR spectroscopy to assess brain tumour tissue remote from the tumour site to ascertain the effects of chemotherapy and radiation treatment. These results should then be correlated with neuropsychological test batteries which include quality of life scales.

Although the role of hyperbaric oxygen treatment for decompression sickness is uncontested its role in the treatment of chronic neurological conditions is controversial. To date this has not been attempted on survivors of brain tumours as part of their treatment. Neuropsychological assessment and quality of life measures on brain tumour survivors before and after hyperbaric oxygen treatment could provide specific measures of its effectiveness on the injured brain and functional states.

Few studies have examined the effect of school disruptions on neurocognitive outcomes. Treatment of brain tumours requires that children miss school for substantial periods of time. The impact of missed schooling on functioning is important in studies with a limited number of

follow-ups. In general, assessment of children at only one point of time has little to offer in advancing the understanding of the development of brain tumours either clinically or conceptually. Individual variability in response to treatment shows that multiple assessments are critical in evaluating outcome.

Precise definitions of "quality of life" and "disability" in future studies would enable comparisons in outcomes across studies. These would provide a better understanding of the relationship of underlying neurocognitive abilities and the interplay among children's pre-existing attributes, the effects of treatment and the social environment.

With the rapid advance in technology the treatment of children with brain tumours may become more sophisticated and require dedicated multidisciplinary innovative team approaches to the role of research. However the volatility of the research environment as the science of oncology becomes more exact means that the original dilemma of weighing the cure of the brain tumour against the sacrifice in quality of life could well lessen over time. As the French mathematician Laplace (1749-1827) stated:

"The theory of probability is only common sense reduced to a calculation, it exhibits with accuracy what reasonable minds feel by a kind of instinct without being able to describe it to themselves. "

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APPENDIX A : Description of Treatment Groups

GROUP 1 - SURGERY TREATMENT GROUP

CASE	ASTROCYTOMA	SHUNT	E.V.D	SURGERY	
	HISTOLOGY			T	S
36	Low Grade	⨯			S
38	Juvenile Pilocytic	⨯		T	
40	Juvenile Pilocytic	⨯		T	
41	Juvenile Pilocytic	⨯		T	
217	Fibrillary	⨯		T	
32	Juvenile Pilocytic	⨯		T	
33	Juvenile Pilocytic	⨯		T	
44	GD I	⨯		T	
43	Juvenile Pilocytic	♦		T	
37	Juvenile Pilocytic	♦		T	
39	Juvenile Pilocytic	⨯		T	
42	Juvenile Pilocytic	⨯			S

n=12

TABLE KEY

- *SHUNT = VENTRICULAR PERITONEAL SHUNT*
- *E.V.D. = EXTERNAL VENTRICULAR DRAIN*
- *T = TOTAL SURGICAL RESECTION*
- *S = SUB TOTAL SURGICAL RESECTION*

GROUP 2 - SURGERY & RADIOTHERAPY TREATMENT GROUP

CASE	TUMOUR TYPE DIAGNOSIS	SHUNT	E.V.D	SURGERY		RADIOTHERAPY - Gy				
	HISTOLOGY			T	S	WHOLE BRAIN	SPINAL	POST FOSSA	CRIB BOOST	WEEKS RT
31	Ependymoma with malignant change	x		T		30	30	20		6
48	Ependymoma with features of a Glioma				S	44	48			6
46	Ependymoma				S	30	40	12		6
16	Ependymoma with malignant change				S	30	30	20		7
35	Brain Stem Glioma	x			S			54		5
49	Low Grade Astrocytoma	x			S			35		6
45	GD I-II Fibrillary Astrocytoma	x			S			16		2
50	GD II Fibrillary Astrocytoma	x			S	54				8
12	Medulloblastoma	x		T		32	32	20		9
20	Differentiating Medulloblastoma		x	T		20	20	32		7
9	Sclerosing Medulloblastoma	x		T		32	32	20	32	7
21	Medulloblastoma				S	23	20	21		6
4	Medulloblastoma				S	27	44	11		5
14	Medullablastoma	x		T		35	30	10		4
23	Medullablastoma	x		T		30	30	24		7
24	Desmoplastic Medullablastoma	x		T		35	30	34		6
27	Medullablastoma	x			S			42		6
17	Medullablastoma			T		30	30	16		6
28	Medullablastoma	x		T		23	47	14		6
34	Juvenile Pilocytic Astrocytoma	x			S			49		6

n=20

TABLE KEY

- *SHUNT* = *VENTRICULAR PERITONEAL SHUNT*
- *E.V.D.* = *EXTERNAL VENTRICULAR DRAIN*
- *T* = *TOTAL SURGICAL RESECTION*
- *S* = *SUB TOTAL SURGICAL RESECTION*

GROUP 3 - SURGERY, RADIOTHERAPY AND CHEMOTHERAPY TREATMENT GROUP

CASE	TUMOUR TYPE DIAGNOSIS	SHUNT	E.V.D	SURGERY		RADIOTHERAPY – Gy					CHEMOTHERAPY		
	HISTOLOGY			T	S	WHOLE BRAIN	SPINAL	POST FOSSA	CRIB BOOST	WEEKS RT	V	CCNU	OTHER
3	Medulloblastoma	×	×		S	32	32	16		10	×	×	
10	Medulloblastoma	×			S	32	32	20		7	×	×	
29	Medullablastoma	×			S	32	48	20	32	6	×	×	
6	Medulloblastoma Desmoplastic Variant	×	×		S	30	30	20		7	×	×	
7	Primitive Neuroectodermal Tumour with Glial & Neuronal Differentiation	×		T		30	30	20	30	7	×	×	Cis-plat-inum
19	Medulloblastoma	×			S	30	30	20		7	×	×	
26	Medulloblastoma	×		T		24	18	20	24	8	×	×	
1	Medulloblastoma	×		T		30	37	10		10	×		
2	Medulloblastoma	×			S	31	35	28		5	×	×	
8	Medulloblastoma	×		T		20	32			7	×		
13	Medullablastoma with Spinal Metastases	×			S	20	21	35		6	×	×	
30	Desmoplastic Medullablastoma with Neoroglial Differentiation	×		T		40	14	14		8	×		Carbo-plat (disc.)
11	Medullablastoma	×			S	35	30	20		8	×		VCR*
18	Medullablastoma	×			S	32	32	20		7	×	×	
22	Medullablastoma				S	35	35	14		7		× (disc.)	
15	Medullablastoma			T		32	32	20		8	×	×	
5	Medullablastoma	×			S	32	32	20		7	×	×	
25	Medullablastoma	×			S	36	42	58		7	×	×	
52	Medullablastoma & Seedling Deposits	×			S	35	38	16		6	×	×	Carbo-plat

n=19

TABLE KEY

- *SHUNT = VENTRICULAR PERITONEAL SHUNT*
- *E.V.D. = EXTERNAL VENTRICULAR DRAIN*
- *T = TOTAL SURGICAL RESECTION*
- *S = SUB TOTAL SURGICAL RESECTION*
- *VCR* = VCR DISCONTINUED*
- *❒ V = VINCRISTINE*
- *❒ POST = POSTERIOR*
- *❒ CRIB = CRIBRIFORM PLATE*
- *❒ disc. = DISCONTINUED*

APPENDIX B – Socio-Economic Status as defined by occupational category

RANK ORDER OF BROAD CASS OCCUPATIONAL CATEGORIES

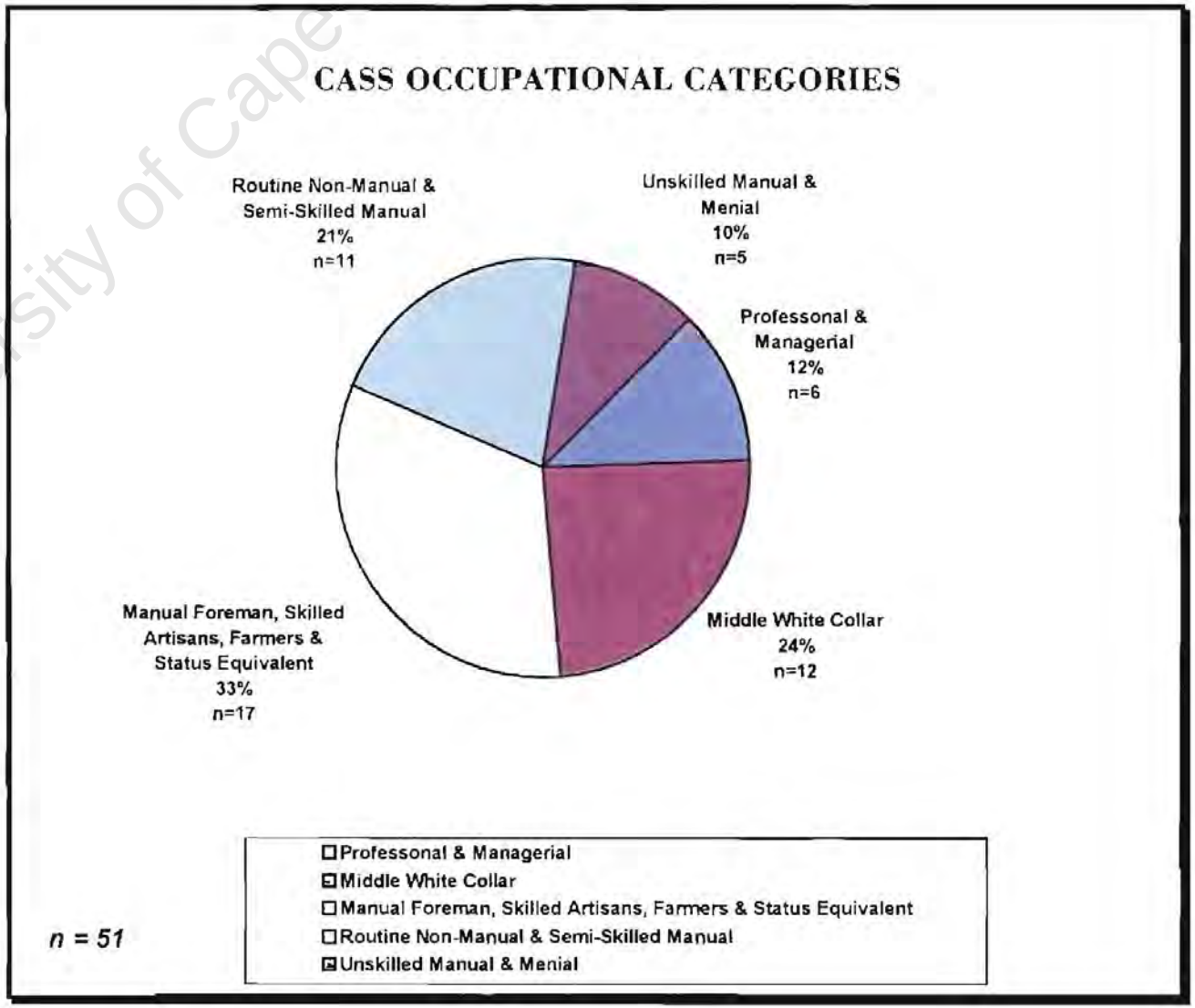
CASS - CENTRE FOR APPLIED SOCIAL SCIENCES

CRITERION FOR CODE INDEX (1 - 5 in Descending Order of Prestige) AMONG 5 CATEGORIES OF OCCUPATIONAL STATUS

Rank & Coding Order	CASS Occupational Category	Rank of Occupation Groups	Grade Intervals of Prestige Scale
1	Professional & Managerial	1-5	82-73
2	Middle White Collar	6-12	72-64
3	Manual Foreman, Skilled Artisans, Farmers* & Status Equivalent	13-16	58-52
4	** Routine Non-Manual & Semi-Skilled Manual	17-18	52-48
5	Unskilled Manual & Menial	19-20	26-20

* White Farmers in South Africa enjoy a higher social and occupational status than is prevalent in most modern countries. It is therefore possible if the case warrants it, to code them as a separate category between Ranks 2 and 3 above. They are included under Rank 3 in the above table.

** This categorisation reflects the general trend for lower non-manual occupations to sink below the traditional manual level in industrialised society.



APPENDIX C – Guidelines for choosing tests Mulhern *et al* (1998)

Proposed Requirements for Practice Standards, Practice Guidelines and Practice Options in Choosing Psychological Tests* (Mulhern *et al* 1998)

Requirements for "practice standards"

1.1 The test has a *high degree* of general clinical acceptance with *overwhelming* scientific evidence of usefulness in the evaluation of children surviving ALL and BT, and

1.2 The test is published and has developmental norms appropriate to the age range of ALL and BT, and

1.3 Evidence of validity with ALL or BT survivors (>2 years from completion of therapy) from one or more publications in a peer-reviewed journal that the test:

- 1.3.1 Discriminates between patients and normal controls (not just test norms), or
- 1.3.2 Discriminates between subgroups of patients with known different risks of impairment, or
- 1.3.3 Demonstrates sensitivity to change in process over time among a sample of patients, or
- 1.3.4 Correlates with abnormalities of the brain seen on CT/MRI

2.0 Requirements for "practice guidelines"

2.1 The test has at least *some* general clinical acceptance and *some* scientific evidence of usefulness in the evaluation of children surviving ALL and BT, and

2.2 Criteria 1.2 and 1.3 under practice standards

3.0 Requirements for "practice options"

3.1 The test has *some* general clinical acceptance with *unknown* usefulness in the evaluation of children surviving ALL and BT, and

3.2 The test purports to assess cognitive processing abilities that appear relevant to learning problems of the school-age child after treatment for ALL or BT

*ALL, acute lymphoblastic leukaemia; BT, brain tumour; CT/MRI, computed tomography/magnetic resonance imaging

APPENDIX D - Multiattribute Health Status Classification

ATTRIBUTE	LEVEL	DESCRIPTION
Sensation	1	Able to see, hear and speak normally for age.
	2	Requires equipment to see or hear or speak.
	3	Sees hears or speaks with limitations even with equipment.
	4	Blind, deaf or mute.
Mobility	1	Able to walk, bend, lift, jump and run normally for age.
	2	Walks, bends, lifts, jumps, or runs with some limitations but does not require help.
	3	Requires mechanical equipment (such as canes, crutches, braces or wheelchair) to walk or get around independently.
	4	Requires the help of another person to walk or get around and requires mechanical equipment as well.
	5	Unable to control or use arms or legs.
Emotion	1	Generally happy and free from worry.
	2	Occasionally fretful, angry, irritable, anxious, depressed or suffering "night terrors."
	3	Often fretful, angry, irritable, anxious, depressed or suffering "night terrors."
	4	Almost always fretful, angry, irritable, anxious or depressed.
	5	Extremely fretful, angry, irritable or depressed usually requiring hospitalization or psychiatric or institutional care.
Cognition	1	Learns and remembers school work normally for age.
	2	Learns and remembers school work more slowly than classmates as judged by parents and /or teachers.
	3	Learns and remembers very slowly and usually requires special educational assistance.
	4	Unable to learn and remember.
Self Care	1	Eats, bathes, dresses and uses toilet normally for age.
	2	Eats, bathes, dresses or uses the toilet independently with difficulty.
	3	Requires mechanical equipment to eat, bathe, dress or use toilet independently.
	4	Requires the help of another person to eat, bathe, dress or use the toilet independently.
Pain	1	Free of pain and discomfort.
	2	Occasional pain. Discomfort relieved by non prescription drugs or self control activity without disruption to normal activities.
	3	Frequent pain. Discomfort relieved by oral medicines with occasional disruption of normal activities.
	4	Frequent pain; frequent disruption of normal activities. Discomfort requires prescription narcotics for relief.
	5	Severe pain. Pain relieved by drugs and constantly disrupts normal activities.

APPENDIX E - Neuropsychological Intake Questionnaire

Name _____ Age _____

Address _____

_____

Tel (h) _____

Tel (w) _____

DOB _____ Sex _____

Race _____ Language _____

Folder # _____ Folder # RT _____

Folder # RXH/GSH _____

Case # _____

DIAGNOSIS

Date & Age at Presentation _____

Date & Age at Testing _____

Time Since Onset _____

Presenting Symptoms

Duration of Presenting Symptoms _____

Vomiting ☐ Headache ☐

Papilloedema ☐ Seizures ☐

Raised ICP ☐ Hydrocephalus ☐ Diplopia ☐

Cranial Nerve Palsy ☐

Speech Dysarthria ☐ Other _____

Affect _____

Loss of Consciousness ☐

Motor : Gait ☐ Ataxia ☐ Broadbased ☐ Other _____

Cerebellar Signs Dysmetria ☐

Dysdiadochinesia ☐

Investigations Pre-Op and Post-Op

X Ray ☐ Date _____

EEG ☐ Date _____

CT Scan ☐ Date _____

MRI ☐ Date _____

Histology ☐ Date _____

Other ☐ Date _____

Pathology Investigations _____

Treatment

Shunt Type _____ Date _____

Complications _____

Revisions ☐ Date _____

Surgery

Date _____

Total ☐ Sub Total ☐ Biopsy ☐

Site : Left ☐ Right ☐ Midline ☐

Exploration : Posterior Fossa ☐ Other _____

Complications Intra-Operative

_____

Complications Post Operative

Infection ☐ Meningitis ☐

Seizures ☐ Speech ☐ Mutism ☐

Visual ☐ Motor ☐ Other ☐

Treatment

Radiotherapy : Date Commenced _____

Site Treated	Tumour Dose	No.Fractions	Days
Head			
Spine			
Posterior Fossa			
Other			

Date Completed _____

Date Discontinued _____ Reason _____

Chemotherapy : Date Commenced _____

Type	Dose	Duration
CCNU		
Vincristine		
Cisplatin		
MOPP		
Other		

Administered : During RT ☐ After RT ☐

Date Completed _____

Date Discontinued _____ Reason _____

Radiotherapy & Chemotherapy Complications Immediate

Neutropenia ☐ Other ☐

Radiotherapy & Chemotherapy Complications Chronic

Hearing Problems : Wax Build Up ☐ Hearing Aid ☐

Visual Problems : Glasses ☐

Growth : Height Date _____ Percentile _____

Weight Date _____ Percentile _____

Late Phase

Recurrence of Tumour _____

Immune System Depletion : TB ☐ Leukemia ☐

Post Operative Treatment/Rehabilitation : Physiotherapy ☐ OT ☐ Speech ☐

Neuropsychological Testing Date : _____

Other : _____

Follow Up

Still in Contact : ☐ Date Last Seen : _____ Next Visit : ____

Discharge Date : _____

Lost to Contact : ☐

Deceased

Date : _____

APPENDIX F - Test Data **Case Number** _____

Demographic History

Parents	Age	Education	Occupation	Employed
Father				
Mother				

Family History

Parents Marital History :

Single Male ☐ Single Female ☐ Living Together ☐ Married ☐

Divorced ☐ Other _____

Siblings

Number_____ Problems ☐ Development ☐ Medical ☐

Education : Failed ☐ Passed ☐ Repeated ☐

Other _____

Religion_____

Parents Hx Medical Problems Seizures ☐ CA ☐

Subject Development

Pregnancy Birth Problems _____

Developmental Delays Walk ☐ Talk ☐ Toilet ☐

School :

Standard _____ Repeated ☐ Failed ☐

School _____

Normal Class ☐ Special Class ☐ Special School _____

Tertiary Training _____

Occupation _____

DG Grant _____

APPENDIX F - Test Results

IQ Test

Type :

SAWAIS ☐ SSAIS-R ☐ ISX ☐ Griffiths ☐ Oasis ☐

FIQ _____

VIQ _____

PIQ _____

Norms Used : SSAIS-R _____

Attention

Digits : Forward _____ Backward _____

Scale Score _____

TMT A _____ P ____ TMT B _____ P ____

Speech & Language

Comprehension Scale Score _____

Similarities Scale Score _____

Speech

Immature ☐ Echocalia ☐ Dysarthia ☐ Perseveration ☐

Memory

Incidental Recall Coding Scale Score _____

Number correctly attributed _____ Number Attributed _____

SSAIS-R Story Scale Score _____

WMS-R

Logical (Story) Immediate P _____ Delay P_____

Visual Immediate P _____ Delay P_____

APPENDIX F - Test Results

Learning

AVLT

Trial 1 Raw Score _____ Expected Score _____

Trial 2 Raw Score _____ Expected Score _____

Trial 3 Raw Score _____ Expected Score _____

Trial 4 Raw Score _____ Expected Score _____

Trial 5 Raw Score _____ Expected Score _____

Total Score :

List B Raw Score _____ Expected Score _____

Trial 6 Raw Score _____ Expected Score _____

Trial 7 Raw Score _____ Expected Score _____

Recognition

Raw Score _____ Expected Score _____

Errors: Intrusions _____ Confabulations _____

Visual Perceptual Information Processing

VMI _____ P

TVPS Visual Discrimination _____ P

TVPS Visual Spatial Relations _____P

Visual Construction Blocks _____ Scale Score _____

Motor Functions

Purdue Pegboard :

Preferred R/L _____ P Non Preferred R/L ___ P Both Hands ____ P

Comments _____

Successive Finger Taps :

Preferred R/L _____seconds Non Preferred R/L _____seconds

Comments _____

Legs Balance 10/20/30 Seconds

Right	_____ seconds		Left _____ seconds
Gait	Ataxia	Yes ☐	No ☐
Tandem Gait		Heel ☐	Toe ☐

Comment _____

Behaviour

WPBIC

Acting Out	Raw Score ____ T ____	Withdrawal	Raw Score ___ T ____
Distractibility	Raw Score ____ T _____	Disturbed Peer	Raw Score ___ T ____
Immaturity	Raw Score ____ T ____	Total	Raw Score ___ T ____

Health Related Quality of Life

MHSC

Sensation	Raw Score ____	Mobility	Raw Score ____
Emotion	Raw Score ____	Cognition	Raw Score ____
Self Care	Raw Score ____	Pain	Raw Score ____
Total Score	_____		

Test Behaviour

Concentration	Persists well ☐		Slightly distractible ☐	
	Very distractible ☐		Gives up easily ☐	
Activity	Appropriate ☐	Listless ☐	Restless ☐	Very Restless ☐
Cooperation/Motivation	Good ☐		Fair ☐	Poor ☐
Affect	Appropriate ☐		Shy ☐	Very Shy ☐
	Tearful ☐		Over Cheerful ☐	Labile ☐

APPENDIX G – Mean Prorated IQ test Scores as per IQ Tests (SAWAIS, SSAIS-R, Griffiths)

	GROUP 1 (n=2)	GROUP 2 (n=9)	GROUP 3 (n=5)
SAWAIS			
FSIQ SD	68.5 14.8	88.44 13.00	75.8 18.96
VIQ SD	68.5 3.53	89.88 9.37	78.6 18.10
PIQ SD	70 28.28	85.66 19.33	74.2 20.04
SSAIS-R			
	(n=8)	**(n=7)**	**(n=9)**
FSIQ SD	84.87 14.97	76.77 23.19	71.33 13.68
VIQ SD	81.75 16.42	77.28 22.74	77.14 14.10
PIQ SD	90 16.42	77.14 15.61	71.44 15.65
GRIFFITHS			
	(n=2)	**(n=3)**	**(n=3)**
FSIQ SD	63 16.97	83.66 30.43	82.66 19.42
VIQ SD	73.55 21.92	96.66 37.07	89.00 17.71
PIQ SD	57.5 16.26	76.6 31.50	77.33 27.02

APPENDIX H : Literature Review Of Neuropsychological And Quality Of Life Outcomes 1975-2000

ARTICLE	DESIGN/ STATS	AGE AT DIAG.	AGE AT TEST	TIME SINCE TX	TUMOUR TYPE / SITE	TREATMENTS	MEASURES	FINDINGS
Onoyama, Mitsuyuki, Takahashi *et al.*, 1975 N = 124	R Descriptive	< 15 yrs		0-16 yrs	• Glioma (97) • Non glioma tumours (27)	Surgery + RT (71) No surgery + RT (53)	Functional Quality of Survival	42 out of 124 children alive. Quality of Survival shows 27 or 69% returned to normal & useful lives i.e. work or school. 21.4% partial disability 12% Stunted growth RT & age 6 – 10 yrs at diagnosis associated with stunted growth. 42 children alive 3-15 years after TX. Despite differences in histology & predilection of tumours, RT can improve quality of survival.
Bamford, Jones, Pearson *et al.*, 1976 N = 30	R Descriptive	14 mths – 15 yrs	9 yrs – 33 yrs	7 yrs 8 mths – 18 yrs	• Medulloblastoma / Ependymoma (8) • Astrocyoma (8) • Cerebellar Astrocytoma (5) • Craniopharyngioma (1) • Optic Glioma (2) • Pineal (2) • Angioma (4)	Surgery Craniospinal RT Cranial RT Treatment not detailed.	History of educational attainment categorized according to Revised Stanford Binet Scales. Functional health & emotional questionnaires	IQ groups: 3=superior, 10=average, 4=below average, 11=subnormal, 2=severely subnormal. Mental handicap may be progressive but cannot be verified. Stature: 76% short. No child TX < 11 years of age had height >10P. Visual: 37% correctable defect, 10% severe visual handicap, 10% blind. Hearing: 3% partial deaf, 3% total deaf. Emotional: 43% problems ranging from aggressive behaviour (11), solitary behaviour (7), emotionally labile (6), insecurity (5), suicide attempts (2) Authors unable to attribute findings to malignant disease, treatment, inadequate rehabilitation or unrelated causes.

Hirsch, Renier, Czernichow *et al.*, 1979 N = 64	R Descriptive	Median 5 yrs	Not given	> 1 yr	• Medulloblastoma (33) • Cerebellar Astrocytoma (31)	Surgery (64) RT (31) Chemotherapy (8) - Chemo included methorexate	WISC Bloom	Medullioblastoma: 31% IQ < 70,27% Bloom category 3 or 4. 82% learning disabilities Astrocytoma: 19% IQ < 70; 19% IQ 70 to 90; 62% FSIQ >90. Emotional & behavioural disorders 59%. .
Broadbent, Barnes & Wheeler, 1981 N = 31	R - over 36 years. Descriptive	3 mths – 14 yrs	Not given	Not given	• Medulloblastoma (9)	Surgery (8) Craniospinal RT (8)	IQ test not specified	22 deceased, 9 alive, of those, 8 tested School: 5=normal school/continuous employment, 2=special school. Mental retardation =3. Age: 2/3 children <3 years of age at TX in mental retardation range. Stature: 50% < 25P Growth hormone secretion normal in 5/6 patients.
Eiser, 1981 N = 42	R Parametric t test	Not given	Not given	Not given	• Craniopharyngiomas (16) • Neuroblastomas/ • Ependymomas (9) • Cerebral Hemispheres (8) • Miscellaneous (9)	Not Reported	WISC WAIS	No effect of tumour site/type. Age: Patients Tx. < 5 years lower scores. Trend for those with hemispheric tumours to have the best & those with craniopharyngiomas to have the worst outcomes.
Danoff, Cowchock, Marquette *et al.*, 1982 N = 38	R Descriptive	Mean 7.9 yrs Range 1-16 yrs	Not given	Mean 9.3 yrs Range 1-21 yrs	• Craniopharyngioma (11) • Optic nerve glioma (6) • Cerebellar Astrocytoma (6) • Medulloblastoma (5) • Midbrain tumours (3) • Cerebral astrocytoma (2) • Ependymoma (1) • Pituitary adenoma (1) • Meningeal Sarcoma (1)	Surgery (37) RT (38)	Bloom Scale WAIS Wide Range Achievement MMPI	Bloom: 89% no disability 55% IQ normal or above 28% dull normal or borderline IQ 17% mentally defective IQ. Unable to assess RT tumour dose and presence of mental retardation as all subjects received same dose of RT. Mental retardation associated with TX before age 3 years & tumours extending into the hypothalamus Behavioural disorders identified in 38% of patients, 59% of mothers and 43% of fathers. 44% of patients with non-parasellar tumours treated before age 11 years

								had endocrine deficiencies. Short stature found in 35% of non-parasellar tumours
Duffner, Cohen, Anderson et al. ,1983 N = 10	R Pre/ post test Descriptive	21 mths – 10 yrs	4 yrs – 22 yrs	3 yrs – 12 yrs	• Medulloblastoma (6) • Ependymoma (1) • Brain Stem Glioma (2) • Cerebellar Astrocytoma (1)	Surgery (10) WBRT (8) RFRT (2) Chemotherapy (10) included methotrexate.	Stanford Binet, WRAT, Bender, WISC-R	50% IQ < 80; 20% IQ > 100. All had dementia, Learning Disability or Mental Retardation. 4 children showed a deterioration of 25 points in FSIQ from pretest, prior to TX, to post test. Authors unable to determine if deterioration in FSIQ due to RT, Chemotherapy or two modalities given in combination.
Kun, Mulhern & Crisco, 1983 N = 30	P Pre TX post TX testing in 10/21 children, Post TX assessment done 10-26 mths after TX. Non parametric chi square	1 yr 9 mth – 15 yrs	Not given	3 yrs	• Posterior Fossa Tumours: • Cerebellar Astrocytoma (7) • Medulloblastoma (5) • Mixed Glioma (2) • Ependymoma (10) • Supratentorial • Cerebral Astrocytoma (7) • Thalamic Astrocytoma (3) • Hypothalamic Astrocytoma (2) • Suprasellar Germinoma (1) • Pineal Malignant Teratoma (1) • Pineal Tumour (1)	Posterior Fossa Tumours Surgery 100% RT 80%, RT+Chemo= 13% (2) Medullo Shunts=93% Supratentorial: Surgery 73% RT, 60%, Chemo = 1 thalamic tumour Shunts =33.3% Sample; Surgery=87% RT =70% Chemo= 10%	McCarthy, PIC, WISC-R, PIAT Bloom	Bloom Classification: 80% no disabilities, 17% partially disabled, 3% totally disabled. IQ: 90+, 63% Mental Retardation 9%. No differentiation between Age at Diagnosis, increased ICP and low IQ. Serial IQ testing (10): Stable IQ (5), Improved IQ (2), Deterioration IQ (2). Deterioration in 1 case associated with seizures. No correlation between shunts & neuropsychological changes. 63% of school going sample in learning disability settings. Borderline Academic functioning (3) attributed to RT and problems with selective attending. Social emotional adjustment in normal range. Abnormal social and emotional functioning in 75% of sample after RT. Authors found factors responsible for impairment difficult to analyse. They suggest a greater than normal risk among children with supratentorial tumours and/or RT.
Chin &	R	18 mths to		2.5 yrs to 13	• Medulloblasoma (10)	Surgery (10)	WISC-R,	Age: Patients < age 4 years at TX

Maruyama. 1984. N = 10	Descriptive	12 yrs		yrs. Median 8 yrs 6 mths		RT (10)	ITPA, WRAT, SDCT, Draw a man, Bender Gestalt, Karnofsky.	major learning problems, those age 5 – 7 years at TX rated as satisfactory passing in school work, those age > 9 years at TX no major impairment. Short stature common but endocrine tests generally negative.
Li, Winston & Gimbrere, 1984 N = 102	R Descriptive	0-15 yrs	Not given	5-47 yrs median 18 yrs	• Astrocytomas (71) • Medulloblastoma (11) • Ependymoma (10) • Other (10)	Surgery (99) WBRT (30) Chemotherapy (3)	Bloom Functional Scale Biographical data	26% mild or no deficits, 24% moderate or severe deficits. Young age at TX. & cerebral astrocytoma are risk factors. Despite diverse performance levels majority had acceptable quality of life. High RT dose not associated with severe impairment. Functional status, educational level +occupation highly positively correlated
Silverman, Plakes, Talent *et al.*, 1984 N = 18	R Control sibling group nearest in age to subject Parametric t test	2.5 yrs to 25 yrs (Median age 7 yrs)	Subjects 9.5 yrs to 31 yrs (median age 14 yrs) Control 7 yrs to 25 yrs(median age 12 yrs) Age diff. Between subjects and controls 0 to 6 yrs.	3 to 7.7 yrs	• Medulloblastoma (9) • Sibling Control (9)	Surgery (9) RT (9)	WAIS, WISC-R. JASTAK wide range achievement test.	Brain tumour patients had lower IQ's than siblings. Children < 8 yrs at TX most severely affected. FIQ, VIQ & PIQ average to low average range. Difference in PIQ worse than VIQ when compared to controls. RT dose no effect on IQ. . Children < 8 years of age at time of TX had lower IQ Educational Quotient of patient group 12 –17 points lower than controls. Arithmetic scores between patients and controls significantly different. Authors state young age and longer time since TX, need to be investigated in prospective serial studies to clarify the effect of RT on IQ scores.
Mulhern & Kun, 1985	P	2 yrs 4 mths to 15 yrs 10	Not given	6 mths	• Posterior Fossa (11) • Astrocytoma (3)	Posterior Fossa Group:	MSCA, WISC-R	Pts. > 6yrs of age improved IQ scores over time, 11% deteriorated in one or

N = 26	Serial testing done after surgery and 6 mths after RT. Parametric t test chi square	mths. Median age = 7 yrs 8 mths			• Medulloblasoma (6) • Mixed Glioma (1) • Ependymoma (1) • Supratentorial (15) • Cerebral Astrocytoma (6) • Cerebral Ependymoma (1) • Neuroblastoma (1) • Craniopharyngioma (1) • Hypothalamic (2) • Pineal (3) • Optic Glioma (1)	Shunt 55% Surgery 100% WBRT &RT 91% Supratentorial Group. Shunt 27% Surgery 80% S+RT 60% RT only 20%	LBC, PIC, WRAT	more parameters. Pts < 6 yrs of age 68% deteriorated in one or more areas of intellectual functioning with prominent difficulties in memory & selective attention. Improvements noted in younger & older age groups over time, although younger age group had greater tendency to IQ deterioration than the older age group. Children < 6 years of age with Supratentorial tumours less likely to improve cognitive performance than those with PF tumours. Second evaluation 23% of children functioning below normal (IQ< 80) with 50% of younger children & 11% of older children in special education. All 4 children with cerebral hemisphere tumours had sensorimotor impairment. No significant effect found for sensorimotor impairment, age, tumour site, raised ICP and RT. Selective attention difficulties found in 27% of children at initial evaluation and 15% at second evaluation. 40%-50% of children had emotional problems. Authors note that causal effects of tumour location, TX, child's reaction to the disease and parental attitudes are unknown, & need further investigation.
Ellenberg, McComb, Siegel *et al.*, 1987.	P 43 pts had Serial Testing; -1 mth after diag.	10 mths to 14 yrs. Mean age 7.5 yrs	N/A	4 yrs	• Fourth Ventricle (22) • Medulloblastoma (11) • Brain Stem glioma (5) • Ependymoma (2) • Malignant Astrocytoma (1)	Surgery (40) RFRT (14) WBRT (23) Chemotherapy (14)	Bayley Scales WISC-R. McCarthy Bloom	Patients with hemispheric tumours most impaired. Amount resected, hydrocephalus & chemotherapy not related to outcome. IQ drop in the RT group evident by 1-3 yrs. Child TX at

N = 73	-Post RT -6mths to 4 yrs post diag. Parametric ANOVA t test multivariate analysis				• Third Ventricle (16) • Craniopharyingioma (5) • Hypothalamic Astrocytoma (3) • Suprasellar epedermoid tumour (1) • Chiasmatic Ependymoma (1) • Pinela Region Astrocytoma (2) • Pinealoma (1) • Malignant Terratoma (2) • Benign Terratoma (1) • Hemispheric (5) • Astrocytoma (4) • Gioblastoma (1)			7ys of age IQ loss over short period of time. Child TX < 5yrs of age with RT had below average IQ at follow up with decline of up to 47 points. Tumour site; Significant decline in IQ for 4th Ventricle tumours over time. 3rd Ventricle tumours maintained IQ. Hemispheric tumours had downward non-significant trend. RT: Multivariate analysis indicated IQ drops attributed to Whole Brain RT rather than tumour site Chemo: No significant differences in mean IQ between groups receiving RT & Chemo (4th Ventricle tumours) and group receiving only RT (3rd Ventricle tumours) Acute hydrocephalus not found to be a potent contributor to long-term IQ changes. No significant difference in IQ score found between partial and total tumour resections. Quality of Life according to Bloom classification; 19% no disability, 33% mild disability, 40 % partially disabled, 9% severely disabled.
Packer, Spasto, Atkins *et al.*, 1987 N = 43	R Parametric Stats type not given	8 mths to 16 yrs 6 mths, mean age 7 yrs 9 mths	Not given	2.5 yrs to 9. 5 yrs Median 5 yrs	• Primitive Neuroectodermal Tumour/ Medulloblastoma (43)	Surgery (43) Craniospinal RT (41) Chemotherapy (13)	WISC-R WART Vineland Pegboard, Finger tapping, Beery VMI, Benton Visual Retention, Coloured Progressive	Performance Score compiled of factors related to neurological functioning and neuropsychological test results. Median performance score for 24 children; Low performance score in 5 children significantly associated with altered mental status at diagnosis, ocular motor deficit at diagnosis, need for permanent shunt & larger T stage of tumour. Children < 7 years of age at

							Matrices, Sentence memory, RAVLT, Selective Reminding, Verbal Fluency.	diagnosis, complicated post operative courses & post operative infection had lower performance scores. Factors statistically associated with low FSIQ; obtunded mental status, partial resection of tumour & shunt placement, Learning, memory and fine motor disabilities found in over half the subjects. The relationship between RT dose and outcome could not be evaluated as most children received similar doses of RT. Authors suggest that the results indicate that perioperative and post operative factors as well as RT needs to be taken into account when evaluating the impact of treatment on outcome.
Roux, 1987. N = 69	R Sibling controls N=20 Sibling controls Sibling controls	Not given Not given Not given Not given	7.5 yrs – 18 yrs mean 11.8 yrs 5.3 yrs – 17.5 yrs mran 10.45 yrs Not given Not given	3.8 to 11.2 yrs mean 7.8 yrs Not given Not given	• ALL (30) • Solid tumour – non hodgkins lymphoma (22) • Wilms tumour (17)	RT to head (30) Chemotherapy included methotrexate (30) Chemotherapy included methotrexate (22) Surgery – nephrectomy	SSAIS Bender Visual Motor Gestalt VMI (Beery) School Achievement	Significant difference between ALL FSIQ 78 & Siblings FSIQ 99 ALL grp children from deprived SES no different to their control siblings, indicating that TX cause of difference in FSIQ scores. Solid tumour FSIQ 96.5 compared to siblings FSIQ 98.4 No significant difference in Bender scores between ALL & siblings and Solid tumour group & siblings. VMI scores for all subjects within age appropriate levels. Poor school performance and high rate of school failure for ALL group. Children under age 5 years at TX

						(17) RT (17) Chemotherapy no methorexate (17)		lower FSIQ than older children. GROWTH – Slow growth for all subjects during TX but growth rate resumed to age appropriate height after TX.
Bordeaux, Dowell, Copeland *et al.*, 1988 N = 19	P Serial Testing: Pre TX Post TX Parametric t test	Surgery Grp 4.6 yrs to 16.3 yrs median 10 .3 yrs Surgery & RT Grp 4.5 yrs to13.5 yrs median 9.8 yrs	Surgery & RT Grp 5.7 yrs to 13.8 yrs median 10.5 yrs	Surgery Grp = 1 mth Surgery & RT Grp = 3 to19 mths median 11 mths	Surgery Grp: • Brain Stem Glioma (1) • Craniopharyngioma (1) • Astrocytoma (5) Surgery & RT Grp • Medulloblastoma ((2) • Astrocytoma (4) • Brain Stem Glioma (1)	Surgery Grp Surgery (7) Surgery & RT Grp Surgery (7) Craniospinal RT (3) WBRT (1) Local to Posterior Fossa (3)	WAIS McCarthy Word Fluency Peabody Picture Vocabulary, WRAT Beery VMI Benton Stereognosis, TMT A&B Finger Tapping Pegboard	Comparisons of pre-therapy findings with normative values using confidence intervals indicated that both groups performed within the average range on most measures. Outstanding deficits at baseline were shown on fine motor, psychomotor and language skills are likely to be attributed to tumour related effects. Comparisons of pre- versus post therapy tests findings indicated no significant interval changes for either grps. Results suggest that Surgery and Radiotherapy are not associated with acute effects on neuropsychological functions.
Duffner, Cohen Parker, 1988. N = 16	P Serial testing pre RT, 1 yr post RT 2 yrs post RT 3 yrs post RT 4 yrs post RT Non parametric Stats not specifed	15 mths to 15 yrs		2 to 5 yrs	• Hemispheric (4) • Midline (6) • Posterior Fossa (6)	Surgery (16) RFRT (3) WBRT (13) Chemotherapy (5)	McCarthy Stanford Binet WISC-R, WAIS-R	Prior to RT 69% of sample FSIQ >90,at year 4 post TX 31% had mean FSIQ >90. Significant declines did not occur until after latency of > 2 yrs. Young age at TX risk factor. 94% of sample learning disabilities classified as attention deficit disorder with and without hyperactivity, visual perceptual disorders, decrease in fine motor coordination & psychomotor speed. Chemotherapy particularly regime of methotrexate, as given to 1 child, is a significant factor in treatment associated dementia. Pt's TX with

								chemotherapy had FSIQ loss of 9-28 points. All children TX with chemotherapy required special class placement compared to only 50% of those TX with RT. Study shows adverse affects of RT on intellectual function may be progressive over several years.
LeBaron, Zelter, Zelter *et al.*, 1988. N = 15	R SEC = middle or upper Class Descriptive	9 mths to 15 yrs 1 mth. Mean 10 yrs 10 mths	6 yrs 10 mths – 17 yrs 7 mths Mean 10 yrs 10 mths	20 mths range 4-104 months	• Medulloblastoma (9) • Cerebellar Astrocytoma (5) • Ependymoma (1)	Surgery (15) WBRT (10) Chemotherapy (1)	WISC-R, WIAS-R, CBCL, Blooms, Halstead Neuropsych. Test Battery, WMSB, PIAT, CBCL.	50% had major neuropsych. Dficits in cognitive flexibility, academic achievement, sensory, perceptual motor functions, and behaviour problems. Patients TX with RT most impaired. Mean FSIQ 77, no diff btwn VIQ & PIQ. Despite posterior fossa location, high rate of higher cognitive deficits found. Authors speculate that this is relevant for those pts receiving RT but puzzling for those not receiving RT. No relationship between Blooms functional rating & psychometric measures.
Mulhern, Horowitz, Kovner *et al.*, 1989. N = 14 SEC lower middle class	P Serial Testing Prior to chemo-Therapy Prior to RT	2 mths to 2 yrs 11 mths Median 19 mths	1.6 yrs to 3.75 yrs	2.9 yrs to 5 yrs Median 41 mths	• Medulloblastoma (8) • Anaplastic Astrocytoma (4) • Glioblastoma (1) • Rhabdoid Tumour (1)	Chemotherapy administered after surgery prior to WBRT Surgery (14) Chemotherapy (14) WBRT (14)	Bayley Scales of Infant Development McCarthy Scales, Vineland Adaptive Behaviour Scales	At initiation of Chemo- therapy < 20% of children had normal performance functioning or mental functioning on age corrected tests; the majority remained stable or declined while receiving chemotherapy. Declining mental development & adaptive behaviour found in 6 children after RT. Only 2 children functioned in normal range for age. Results indicate that neurodevelopmental progress is a function of multiple factors, including neurologic & sensory motor deficits associated with the tumour, surgical intervention, and chemotherapy that

	Post RT Descriptive		Not given					antedated RT. Delaying RT will not necessarily improve child's functional status.
Packer, Sutton Atkins *et al.*, 1989 N = 32	P Serial Testing Surgery RT Chemo Grp: Baseline (post-surgery, prior to RT) Year 1 Year 2 Surgery Grp Baseline (post-surgery) Year 1 Year 2 Non Parametric chi square or Wilcoxon Linear regression	1.10 yrs to 18 yrs Median 7.7 yrs 1. 6 yrs to 16.8 yrs Median 7.7 yrs	Not given	Median 2 yrs	• Malignant Primary CNS Tumours • Medulloblastoma/PNET (15) • Pineal tumours (2) • Suprasellar Germinoma (1) • Comparison Group • Cerebellar Astrocytoma (14)	Malignant CNS Tumour Group: Surgery (18) CRT (18) Chemotherapy to selected cases. (13) Comparison Group: Surgery (14)	Bayley Stanford Binet, WISC-R WAIS-R, WRAT, finger Tapping Grooved Pegboard, Beery VMI, Coloured Progressive Matrices, Token Test, Rey Complex Figure, Selective Reminding, Sentence Completion.	Mean FSIQ of Surgery, CRT & Chemo Grp declined from 105 at baseline to 91 at Year 2. No significant difference shown between VIQ & PIQ for either Grp. Mean FSIQ of Surgery Grp did not show a fall in any cognitive parameter over time. Fine motor speed & dexterity were impaired at both baseline and Year 2. Visuomotor functions were impaired at initial testing and at follow up. Visuospatial, memory & language functions relatively preserved. Only 1 child in special education, the other 8 in regular classroom. In Surgery, RT & Chemo Grp decline in FSIQ at baseline & Year 2 was inversely correlated with young age. Children < 7 yrs of age at diagnosis had a mean decline of 25 points in 2 yrs post TX. Surgery, RT & Chemo Grp at 2 yrs post TX had deficits in fine motor, visual spatial skills & memory difficulties. These deficits worsened over time. School performance was adversely affected by young age at TX. Older children maintained regular

								school placement with help but younger children commenced school in special education facilities at Year 2. Authors unable to evaluate the role of chemotherapy, although no evidence was shown that the chemotherapy protocol (CCNU,vincristine & cisplatinium) increased the incidence of intellectual functioning.
Riva, Pantaleoni & Milani, 1989. N=30	R Matched Control siblings & cousins Parametric t test	Mean 6.25 yrs	Not given	Medulloblasoma Mean = 5 yrs Astrocytoma Mean = 3.25 yrs	• Medulloblastoma (8) • Cerebellar Astrocytoma (7)	Surgery (15) WBRT (8) Chemotherapy (8)	WISC-R, CPT, Trails A & B	Both patient groups worse on IQ & attention measures than controls. Only medulloblastoma patients showed severe deficits (mean IQ=74.6). No RT astrocytoma grp IQ average range (106).
Sutton, Packer, Siegel *et al.*, 1989 N = 47	P Comparitative Grps Surgery, RT & Chemo Grp Surgery Grp Serial Testing Baseline prior	Surgery RT & Chemo Grp: 18 mths to 18 yrs Median 7.8 yrs Surgery Grp 18 mths to 16.8 yrs Median 7 yrs	Not given	2 yrs	• Medulloblastoma (20) • Primary Pineal Tumours (4) • Suprasella Germinomas (2) • Cerebellar Astrocytoma (21)	WBRT (26) Chemotherapy (not specified). Astrocytoma Surgery (21)	Bayley, Stanford Binet, WISC-R, WAIS-R, Grooved Peg Board, Beery, Coloured Progressive Matrices, Token Test, Selective Reminding, Sentence Repetition, RAVLT, WRAT, PIC.	2 yrs post diagnosis significant drop in full-scale IQ, verbal IQ & non-verbal IQ in RT group. Not evident in Surgery group. Decline in FSIQ significantly correlated with age. Children age < 7 yrs. at TX median IQ = 87 compared to 102 for older children. Children age < 3 yrs at diagnosis are devastated those > 10 yrs at diagnosis are relatively spared. IQ deficits declined progressively in RT group over 2-year period. RT dose did not correlated with IQ change. Hydrocephalus, post – operative complications or chemotherapy did not correlate with overall IQ or change in IQ. Fine motor speed & dexterity abnormal in both groups. No deterioration over time. Memory functions deteriorated in 38%

	to surgery. Post TX Year 1 Year 2 Non Parametric Stats not specified							RT group at 2 yrs post TX. Particularly in those age< 7yrs at TX. Academic performance declined over time in RT grp & need for special schooling occurred.
Brookshire, Copeland, Moore *et al.*, 1990 N = 31	P Parametric ANOVA	Sample 3.4 yrs to 16.3 yrs Mean 10 .1 yrs Cerebral Hemis-Phere Grp Mean 12.8 yrs Supra-tentorial Grp Mean 9.6 yrs Infraten-torial Grp Mean 8 yrs		1-3 days prior to surgical treatment	• Cerebral Hemisphere (7) • Infratentorial (12) • Supratentorial midline (12)	All subjects tested prior to any form of TX	WISC-R McCarthy Scales WRAT Token Test Verbal Selective Reminding. Non Verbal Selective Reminding, VMI, Coding subtest, Finger Tapping Pegboard TMT A&B F-A-S Word Fluency	Total group performed within average range on all neuropsychological domains When subjects grouped according to tumour location: 71% cerebral hemisphere grp, 64% supratentorial grp, 73% infratentorial grp performed within or above normal limits. Apart from executive domain in which cerebral hemisphere grp's performance was statistically poorer than the other tumour grps. Children with infratentorial tumours had symptoms of headache & nausea for briefest period, < 3 months. Cerebral tumours had the longest period. Hydrocephalus occurred in 67% of infratentorial tumours, 58% of supratentorial tumours but not in cerebral tumours. Children with hydrocephalus scored lower on measures of intelligence, executive skills, visual motor abilities & fine motor skills. 50% of infratentorial group had cranial nerve

								deficits. 67% of infratentorial group had cerebellar signs. Tumour location & symptom duration correlated with executive domain score. Significant correlation between cerebellar signs & visual motor & fine motor domain scores. Age did not correlate with any measure, except in executive domain indicating age did not contribute to differential performance. Over representation of older children in cerebral group confounded results
Hoppe-Hirsch, Renier, Lellouch-Tubiana *et al.*, 1990 N = 120	R Descriptive	1yr to 15 yrs	Not given	55 pts followed up for 5 yrs 13 pts followed up for 10 yrs	• Medulloblastoma (55)	Surgery (55) WBRT (55) Chemotherapy (unclear)	IQ (unspecified) Functional rating of Quality of Life	Survival – 60% 5 year survival rate. 53% 10 year survival rate. Surprisingly survival better in children TX < 6 years of age than older children. 5 yrs post TX, 58% had IQs < 80 & 40% normal academic level. 10 yrs post TX only 13 pts from original grp tested – 2/ 13 (15%) pts IQ > 80; 5/ 13 pts IQ 60-80; 6/13 pts IQ < 60. Children age < 3 yrs at TX had worst outcomes. Emotional & behavioural disorders found in 47% of pts 5 yrs post TX & worsened to 78% at 10 yrs post TX. 60% of pts attended special school 10 yrs post TX and no pt had normal employment. Neurological sequelae such as hearing loss and epilepsy became worse at 10 yrs post TX whereas ataxia & limb weakness improved slightly & cranial nerve deficits abated.
Jannoun & Bloom, 1990	R Parametric	9 mths to 15. 9 yrs Median 9.2	7 yrs to 32 yrs Median	3 yrs to 20 yrs Median 10 yrs	• Supratentorial (39) • Infratentorial (23)	Surgery (52) WBRT (13) RFRT (49)	WISC-R, WAIS, Bloom	112 children deceased, 89 alive, 67 tested. IQs < 80 in 22% of patients.

N = 201		yrs	19 yrs			Chemotherapy (number of cases not specified)	Functional Disability Scale	Supratentorial sites, hydrocephalus at presentation, hypothalamic involvement, RT & younger age at TX were risk factors. 26% of pts with supratentorial tumours FSIQ < 80 compared with 17% in infratentorial grp. Quality of Life – 72% of supratentorial grp mild to severe neurological and physical disabilities as compared with 44% in infratentorial grp Pts who had RT to whole neuraxis did less well in terms of IQ. 31% had IQ < 80. Of those cases 8 also received chemo as well as surgery & RT. No significant differences found between those whose TX included chemo and those who did not receive chemo. Long-term outcome after TX shows 60% of patients have normal or higher IQ & 57% leading normal lives without neurological or physical disability.
Lannering, Marky, Lundberg *et al.*, 1990 N = 116	R Subgroup (n=23) mild or no disability compared with Control Grp (n=60) Parametric chi square	Under the age of 17 yrs	7 yrs to 31 yrs Mean 19 yrs	5 yrs to 16.5 yrs Mean 10.3 yrs	• Supratentorial (27 in total but 11 sited in midbrain & 16 in hemispheres) • Infratentorial (29)	Surgery (53) RT according to site: Supratentorial (12) Infratentorial (10) Chemotherapy to malignant tumours (16). Type/site not specified	WISC, WAIS (Swedish version), Claesson-Dahl Test of memory & learning	48 deceased, 68 survived, 56 subjects tested. RT most important factor for cognitive sequelae, whereas psychological emotional sequelae more frequent for supratentorial tumours. Pts with no disability (20) – survivors of cerebellar astrocytoma. Pts with mild disability (17) – slow learners, had epilepsy, and /or ataxia with mild dysfunction. Pts with moderate (10) & severe (9) disability had mental retardation, psychological-emotional & visual impairment. RT given at age < 6yrs associated

	t test ANOVA							with slow learning or mental retardation. **Matched controlled social assessment**: fewer pts were married, only one pt had a child, less pts completed high school. Pts who lived active lives mean quality of life score of 73 (range 40-100). Time to diagnosis, age, papiloedema at diagnosis and preoperative conditions not related to disability at follow up. Self reported quality of life was not related to severity of disability but to psychological-emotional sequelae.
Dennis Spiegler, Fitz, *et al.*, 1991 N = 46	R Parametric Multiple regression Analysis	1.3 yrs to 15.4 yrs Mean 8.1 yrs	6.4 yrs to 20.8 yrs Mean 13.7 yrs	Mean 4.08 yrs	• Craniopharynglioma (50%) • Astrocytoma (13%) • Medulloblastoma (13%) • Germinoma 7% • Other cysts 7% • Neuroectodermal 2% • Lipoma 2% • Dermoid 2%	Surgery (45) WBRT (9) RFRT (14) Chemotherapy (3)	WISC, WISC-R, WAIS, WAIS-R, Goldman-Friscoe-Woodcock Auditory Memory Battery	CT Scan reconstruction of 88 brain regions coded with respect to tumour and related damage. Multiple regression procedures established patters of brain damage predictive of memory deficits. Two forms of memory revealed non overlapping focal neuro anatomical substrates; Memory for serial order pictures involved the limbic system and hypothalamic –pituitary axis, and working memory involved the pineal-habenular region & anterior, & medial thalamic nuclei. Memory for semantically based word pictures unaffected by tumour location.
Dennis, Spiegler, Hoffman, *et al.*, 1991 N = 46	R Parametric Multiple regression Analysis	1.3 yrs to 15.4 yrs Mean 8.1 yrs	6.4 yrs to 20.8 yrs Mean 13.7 yrs	Mean 4.08 yrs	• Craniopharynglioma (50%) • Astrocytoma (17%) • Medullobiastoma (13%) • Germinoma 7% • Other cysts 7% • Neuroectodermal 2% • Lipoma 2% • Dermoid 2%	Surgery (45) WBRT (9) RFRT (14) Chemotherapy (3)	WISC, WISC-R WAIS, WAIS-R Goldman-Friscoe-Woodcock Auditory	Tumours classified according to both histology and regions of the brain. This complex coding is an attempt to analyse the lesion and the invasion of the lesion into other anatomical sites. Memory impairment was found in the entire sample. IQ based regression model accounted for less than a

							Memory Battery	quarter of the variance & showed that VIQ is not the main determinant of memory test performance. Age at tumour onset accounted for 13% of the variance in sequence memory and not the determinant of performance in the task. Memory and time from tumour diagnosis to test not significant.
Mostow, Byrne, Connelly *et al.*, 1991 N = 389	R Matched Sibling Controls N=479 Parametric t test odds ratio calculated.	Average 11.3 yrs Siblings 12.3 yrs	Average 32 yrs Siblings 33.2 yrs	At least 5 yrs	• 342 Brain Tumours Type :- • Astrocytoma 56% • Glioma 8% • Ependymoma 8% • Medulloblastoma 7% • Other 21% Site :- • Supratentorial 18% • Infratentorial 39% • Not specified 36% • Extracranial 7%	Surgery 94%, RT 54%, RT & Chemo-therapy 2%, Chemotherapy 1%.	Quality of Life Dimensions: Alive/Dead Employment Conditions affecting work Drive car Income Health Perception	47 pts. Deceased of those 44 pts died directly as a result of the primary tumour, treatment &/or a recurrence. 342 subjects survived. 15% never employed. 37% health condition led to job change or work stoppage The health parameters: Emotional problems 12% sight problems 24% hearing problems 8%. Unable to drive cars 13%. Excellent health 38% poor health 5% never married 42% Unfavourable quality of life more frequent in males than females in supratentorial tumours than infratentorial & those who receive RT. Age – young age at diagnosis significantly correlated with risk of never being employed, lower level of final education or never marrying. No histological diagnosis was consistently associated with increased risk for any of the outcomes when survivors were compared to matched controls. Matched analysis less meaningful as most survivors had astrocytomas. Medulloblastoma survivors were most likely to have had every one of the unfavourable

								outcomes listed. Increased risk of death associated with RT TX.
Dennis, Spiegler, Obonsawin, *et al.*, 1992 N = 46	R Parametric Multiple regression analysis	1.3 yrs to 15.4 yrs Mean 8.1 yrs	6.4 yrs to 20.8 yrs Mean 13.7 yrs	Mean 4.08 yrs	• Craniopharynglioma (50%) • Astrocytoma (17%) • Medulloblastoma (13%) • Germinoma 7% • Other cysts 7% • Neuroectodermal 2% • Lipoma 2% • Dermoid 2%	Surgery (45) WBRT (9) RFRT (14) Chemotherapy (3)	WISC, WISC-R WAIS, WAIS-R, Goldman-Friscoe-Woodcock Auditory Memory Battery	VIQ but not PIQ varied positively with age at RT TX. Severe deficits in serial position memory occurred with impaired hormone function and older age at tumour onset. Severe deficits in working memory were associated with RT & principle tumour site that involved the thalamic /epithalamic brain regions. The authors discuss that the results are not fully understood and the data highlight the need for tumour markers that include maturational rate, hormone status, RT history and principle site of tumour.
Feeny, Furlong, Barr *et al.*, 1992 N=41	R Descriptive	Not given	Not given	Not given	• ALL, Wilms tumour, & neuroblastoma on treatment (20) • ALL, Wilms tumour & neuroblastoma (8) off treatment • Brain tumour children on treatment (13)	Treatment not stated but according to Diagnostic categories	Multiattribute Health Status Classification	Independent ratings by 6 clinicians found that 61% were in agreement as to the level of morbidity. Change of one level required in 89% of cases. Emotion & pain were the attributes that caused the most disagreement. Results supported the hypothesis that patients on TX suffered greater burdens of morbidity than those off TX. Brain tumour patients had lower functional abilities than ALL, Willms tumour or neuroblastoma patients.
Hudson & Murdoch, 1992. N=3	P Serial testing: After to RT & 6 month intervals x 2	Subject 1-10 yrs 6 months, Subject 2 - 7 yrs 2 months Subject 3 5 years 9			• Medulloblastoma	Surgery (3) RT (3)	Test of Language Development-Primary or Intermediate. Boston Naming Test, Token Test.	Pattern of language recovery after treatment in 3 subjects was variable. None of the subjects showed language deficits at base line testing after surgery and during RT Thus deficits attributed to RT treatment. Authors state that different ages at diagnosis may have contributed to

	Descriptive	months						varying outcome. Severe semantic lexical deficits detected immediately post treatment improved dramatically in the first six months after treatment.
Moore, Ater & Copeland, 1992 N = 28	R Subjects assigned to comparable grps according to TX : S+Chemo +RT (RT) Or S+Chemo (No RT) Parametric t test on continuous variables, Fisher's exact test on categorical variables.	1 mth to 2.9 yrs Mean 1.6 yrs	3.6 yrs to 26.25 yrs Mean 8 yrs	Average 6.2 yrs	• Medulloblastoma (10) • Astrocytoma (grades I & II, - sited in midline & cortical region (13) • Ependymoma (3) • Pinealoma (1) • Primitive neuroectodermal tumour (1)	Surgery (28) Cranial Irradiation (14) No cranial irradiation (14) Chemotherapy (16)	McCarthy, Stanford Binet, WISC-R. WART Peabody Individual Achievement Test Verbal Fluency- FAS Non Verbal Selective Reminding Beery VMI Finger Tapping Pegboard TMT A&B	64% in **No RT** group FSIQ average or above average. 70% in **RT** group below average, 4 scores mentally retarded. **RT** group significantly lower PIQ than VIQ. **No RT** group showed opposite but non significant pattern Mean scores for **RT** grp lower than for **No RT** grp in all areas assessed & were significantly lower in intellectual, memory, attention, motor, and visual spatial skills with relative preservation of language abilities. Mean scores for **No RT** grp within average range in all cognitive areas except visual spatial skills which were significantly below age based normative means Endocrine deficits & growth retardation more prevalent in **RT** grp. Correlations between Age at Time of RT & neuropsychological functioning not statistically significant. Possibly due to the fact that children treated at an older age were not represented. Thus a larger sample was defined (58) composed of children TX with RT across a broader age range (11 mths to 18 yrs 4 mths, mean 7.3 yrs) In this analysis statistically significant correlations for general intellectual performance, academic and visual spatial domains, indicating that children who were older at the time of

								RT had higher scores in these skills.
Radcliffe, Packer, Atkins, *et al.*, 1992 N = 19 Sample dropped to N=15 at year 2& 3 & N=7 at year 4.	P Serial Testing: Baseline Yr 1 Yr 2 Yr 3 Yr 4 Non Parametric Wilcoxon, Spearman rank	1.6 yrs to 19 yrs Median 8 yrs	Not needed	4 yrs	• Medulloblastoma/ PNET (14) • Germinomas (5)	Surgery (19) RT (19) Chemotherapy (14)	Bayley, Stanford Binet, WISC-R, WAIS-R	Mean FSIQ fell significantly from 104 to 92 at follow up. Decline in FSIQ occurred between baseline and year 2. None could be documented between years 2 and 4. Age inversely correlated with change in FSIQ over time. Children < 7 yrs at diagnosis mean FSIQ loss of 27 points. Child > 7 yrs. at diagnosis showed no significant decrease. All children age < 7 yrs at diagnosis received special education. 50% age > 7 yrs at diagnosis received supplementary education. No difference in FSIQ scores between children who were TX with Chemotherapy & those who not TX with Chemo. Disease location, extent of disease & post op complication did not affect outcome.
Silber, Radcliffe, Peckham *et al.*, 1992 N = 48	P Serial Testing 2 yrs before RT First & last test separated by at least 2 yrs. Parametric Linear regression model Type 1 & Type 11 errors controlled by	PNET Mean 7.06yrs ALL Mean 4.90 yrs	PNET Mean 7.19 yrs ALL Mean 4.85 yrs	Mean 3.6 yrs 1.41 yrs – 18.57 yrs	• PNET (24) • ALL (24)	Surgery (24) WBRT (24) Chemotherapy (?)	WPPSI, WISC, WISC-R, WAIS. WAIS-R Stanford binet Bayley Test, McCarthy Scales.	Higher RT doses related to greater decline in IQ. Multiple linear regression model showed that children who receive 18GY radiation to the brain score 12.3 IQ points higher than those children who received 36 GY after correcting for age at TX The younger age at TX the lower the IQ. An average increase of 11.9 IQ points between age 3 – 10 years when first irradiated.

	Least Detectable Difference							
Barr, Furlong, Dawson *et al.*, 1993 N = 55 Prospective N=10 Retospective	P Classification filled in by consortium of 1 nurse & 4 physicians independently. Non Parametric Spearman Rank Logical Regression analysis	Std Risk 2.1 yrs to 8.11 yrs High risk: 1 yr - 2 yrs or > 9 yrs Long Term: Not given	Not given Not given Not given	in regular follow up in regular follow up 15-20+ yrs	• Standard Risk Acute Lymphoblastic Leukemia ○ (25) • High Risk Acute Lymphoblastic Leukemia (30) • Long Term survivors (10) (R study)	Both Std Risk & High-Risk Grps (44) RT varied doses. Chemo excluded methorexate, other details not given. Long Term: Not given	Multiattribute Health Status Classification	Std Risk: 60% no morbidity, 8% co-morbidity. 20% cognitive deficits. High Risk: 30% no morbidity, 23% co-morbidity. (< 26% emotional morbidity, > 36% cognitive morbidity) Long term: 50% morbidity Std & High Risk Grps: positive correlation btw emotional & cognitive deficits as well as radiation dose & emotional deficits. Negative correlation btw age at diagnosis & emotional deficit.
Cohen, Packer, Siegel *et al.*, (1993) N=39	R Descriptive	< 2 yrs	Not given	4.25 yrs to 21 yrs	• Primary Brain Tumours	Surgery +Chemo Grp (9) RT alone or RT + Chemo Grp (11) Benign tumours TX not given (12) Other Grp various combinations of TX (7)	IQ test not specified Clinical neurological examination School reports	Surgery+Chemo Grp: FSIQ 130-72 RT alone/RT+Chemo: FSIQ: Average = 1; Below average =3; Borderline = 1; Mild mental retardation= 2; Profound delay =2 Benign Grp: IQ range 114—75. Not tested =9 of which 8 regular class & 1 learning disabled. Overall 41% have normal neurological &IQ functioning, 13% borderline IQ or a degree of visual loss, 54% significant sequelae (IQ<80, blindness or paresis.) Pt's TX with chemotherapy alone or chemo-therapy and delayed RT had better IQ's than those TX with local RT. Quality of Life affected by tumour location, preoperative status, surgical complications, increased intracranial pressure, post operative infection &

								treatment.
Feeny, Leiper, Barr *et al.*, 1993 N=69	R Descriptive	Mean 5.9 yrs	8-25 yrs	Mean 9.3 yrs	• High risk ALL (69)	Chemotherapy including methorexate & RT (69)	Multiattribute Health Status Classification System	From clinical records: 42% no deficits, 32% deficits in one attribute. 26% two or more deficits. Survivors had greater level of morbidity than general population in Great Britain (GB). 7% ALL reduced sensation compared to 1.9% children in GB. 28% ALL deficits in emotion, GB children have 2.1%. 39% ALL deficits in cognition GB children have 0.9%. Canadian population had poorer vision compared to ALL survivors & lower cognition compared to GB. Relative to population norms for GB, ALL survivors had greater morbidity. Proportion of ALL survivors who enjoy normal health is similar to the Canadian general population.
Billison, Walker, 1994 N=48	P Non Parametric Wilcoxon	Not given	2-17 yrs	1 mth – 12 yrs	• ALL (17) • Brain tumour (7) • Non Hodgkin's lymphoma (6) • Rhabdomyosarcoma (6) • Wilms tumour (4) • Hodgkin's disease (2) • Neuroblastoma (2) • Osteosarcoma (1) • Hepatoblastoma (1) • Teratoma (1) • Ewings Sarcoma (1)	Not specified	Multiattribute Health Status Classification System	Questionnaire completed by parents of children <8 yrs, parents & children of patients 8-14 yrs, patients only if > 14 years. Thereafter doctor filled all the questionnaires. Assessment completed by patient/parent and doctor in 48 or 76% of the subjects. 33% of parent/patients & 40% of doctors found no deficits. Statistically analysis showed no significant differences between the two health status scores.
Gajjar, Mulhern, Heideman *et al.*, 1994	P Serial Testing After TX 2.2 yrs	.9 yrs – 3 yrs Median 2 yrs	Not given	4 yrs – 8.9 yrs Median 7.5 yrs	• Medulloblastoma (13)	Surgery (13) Chemotherapy (13- 0f these early termination of chemotherapy	Vineland WISC-R	6 children are alive 4 yrs to 8.9 yrs after the treatment. Neurodevelopmental scores tended to be below age norms at diagnosis, Scores improved during

N = 13	6.7 yrs Descriptive Kaplan Meirer estimate of overall survival rate.					in 11) RT (13)		chemotherapy in verbal & /or motor scales but then decreased during post TX. FSIQ at last follow up = 50 – 96, mean 70, significantly lower than age adjusted norms. Only 2 children completed Chemo & received RT. 11 children had spread of tumour during Chemo. Of these 6 children complete response to RT of which 3 are alive. Following incomplete response to Chemo, RT appears to produce long-term disease free survival but neurodevelopmental deficits frequently occur.
Johnson, McCabe, Nicholson *et al.*, 1994 N = 32	R Non Parametric Kruskal Wallis Test, chi square, Mann Whitney & Fisher's exact test	1.7 yrs – 15.9 yrs Mean 4.7 yrs	9 yrs – 35 yrs Mean 15.5 yrs	Not given	• Medulloblastoma (32)	Craniospinal RT (100%) Methotrexate Chemotherapy (23%)	WISC-R, WAIS-R, WRAT-R, Hooper Visual Organisation Test, Purdue Peg Board, WCST, Benton Visual Retention WMS, RAVL, Trails A & B, CBCL, Symptom Checklist, VABS HSPP	Only 13 of 32 pts tested. IQ < 90 for all pts. Mean IQ, achievement test scores in reading, spelling & maths higher in shunted pts than non-shunted pts. Perceptual motor task performance below average in > 50% of sample. Motor dexterity more severely affected than perception. Learning problems & delayed physical growth & development found in majority of sample. Behavioral problems in 38% of sample reported by parents. Attention & organisational skills moderately to severely impaired in 46%. Total tumour resection significantly better than partial resection pts. Moderate to severe deficits worse in visual memory, 85% than verbal memory 46%. 13 of 23 children in special education programs. 78% of children had learning problems. 74% delay in physical growth or development. 22%

								needed help in bathing or dressing.
Kao, Goldwein, Schultz *et al.*, 1994 N = 28	P Serial Testing Baseline prior to surgery; After RT Year 1 Year 2 Year 3 Year 4 Non Parametric Pearson's Product Moment, chi square, t test, Logistic Regression Analysis	1.5 yrs – 16.4 yrs Median 6.8 yrs		.6 yrs – 6 yrs Mean 3.6 yrs Average Time from baseline 1.2 yrs 2.6 yrs 3.6 yrs 4.9 yrs	• Medulloblastoma (28)	Surgery (28) RT to various sites (28) Chemotherapy (20)	Bayley, Stanford Binet, WISC, WISC-R	Presence of adverse factors i.e. neurologic deficits, meningitis or shunt infections, repeated surgery correlated significantly with IQ deficits after treatment. Presence of adverse factors & age < 6 yrs correlated significantly with FSIQ decline after treatment. Significant correlation between age < 8 yrs & occurrence of adverse perioperative factors. No correlation between WBRT dosage & neurocognitive deficits. No correlation between shunt placement prior to RT & neurocognitive deficit. Small number of subjects precluded determination of whether IQ losses represent the loss of prior skills or decreased ability to learn new tasks or process information.
Moore, Ater, Needle *et al.*, 1994 N = 42	R 3 Groups matched by SES, Age, Race, Sex, & Brain Tumour diagnosis Descriptive &	Not given	Grp 1 6.5 yrs – 13.5 yrs Grp 2 4.8yrs – 13.6 yrs	Prior to TX	Grp 1 • Neurofibromatosis (14) Grp 2 • Brain Tumours of mixed origin: • Medulloblastoma (6)	Surgery to more than half children in Grp 2 Brain tumour Grp. Otherwise all children tested prior to TX	WISCR-R WRAT –R Verbal Fluency, Beery VMI, Finger Tapping, Grooved Pegboard, TMT A & B	Neurologic Results: Grp 1 essentially normal results: Grp 2 high incidence of hydrocephalus, cerebellar abnormalities and moderate incidence of cranial nerve abnormalities and motor abnormalities. Grp 3; majority no abnormalities with about a third of the Grp with difficulties in motor functions, cerebellar

	Parametric Multivariate analysis type 1 error corrected using Bonferonni correction		Grp 3 4.75 yrs – 14.3 yrs		• Cerebellar Astrocytoma (3) • Optic Glioma (3) • Brain Stem Glioma (1) • Craniopharnygioma (1) Grp 3 • Neurofibromatosis plus brain tumour • Optic Glioma (9) • Cerebellar Astrocytoma (2) • Brain Stem Glioma (2) • Hypothalamic Astrocytoma (1)		Freedom From Distractibility Quotient of WISC-R	abnormalities, cranial nerve difficulty & hydrocephalus. Significant differences found in domains of academic achievement, memory, visual spatial, distractibility. Overall Grp 2, the brain tumour only Grp, scored significantly higher than the other Grps in intelligence, academic achievement, visual spatial ability and freedom from distractibility. Memory tests scores were on a par for Grp 1 & 2 with Grp 3 having the lower score. Results suggest that as a group children with brain tumours have normal cognitive abilities before TX with RT or Chemotherapy despite a higher number of neurosurgical procedures and neurologic abnormalities.
Mulhern, Heideman, Khatib *et al.*, 1994 N = 16	P Parametric t test	2.1 yrs – 14.3 yrs. Median 4.1 yrs	Not given	1.5 yrs – 5.6 yrs	Brain Stem Glioma:- • Dorsally Exophytic/ Juvenile Pilocytic Astrocytoma (10) • Fibrillary Astrocytoma (1) • Diffusely Infiltrating (5)	Dorsally Exophytic Surgery (11) RT (4) Diffusely Infiltrating: Surgery (4) RT (5)	WISC-R McCarthy Scales Beery VMI Vineland Child Behaviour Scales	Presenting symptoms included ataxia, vomiting, headache, 6th or 7th carnial nerve palsy with median duration of presenting symptoms lasting 5.5 months prior to diagnosis. FSIQ ranged from 58 to 123 (median 94) FSIQ scores not correlated with age at diagnosis, degree of tumour resection, Severity of IQ problems & severity of neurologic problems showed a significant inverse association. The need for a VP shunt not associated with intellectual delay. In general all the children had a low incidence of intellectual impairment & an adequate quality of life as defined by standardized measures of academic achievement and behavioural adjustment.

								Although children with exophylic tumours TX with surgery only appear to have the most favourable neuropsychological outcomes, this advantage was more likely a result of fewer neurological deficits than the absence of RT. No advantage in sparing of neuropsychological functions found by RT Dose i.e. hyperfractionated as opposed to conventional RT to the brain stem.
Nishiyama, Funakoshi, Izumato *et al.*, 1994 N = 2	R Case report Monozygotic-twin. Serial Testing Descriptive	3.75 yrs	7.4 yrs 8.4 yrs 9.75 yrs	3.6yrs 4.6 yrs 6 yrs	• Medulloblastoma (1) • Control Monozygotic Twin (1)	Surgery – Total (1) Postoperative chemotherapy (1) CNS Radiation (1)	WISC-R Tree Test	Significant differences between the patient and control on all three administrations in FSIQ (67 versus 102; 70 versus 98; 64 versus 93) VIQ (80 versus 114; 78 versus 112; 74 versus 98) PIQ (58 versus 88; 66 versus 83; 59 versus 87). Lack of detail in the Tree Test of the patient compared to her twin indicated mental deterioration. Growth: The patient's radiated spine & also the non radiated upper and lower limbs were shorter than her twin's.
Seaver, Geyer, Sulzbacher *et al.*, 1994 N = 18	R Non Parametric chi square, Pearson Product Moment.	1. 25 yrs – 15 yrs Mean 6 yrs	7 .4 yrs – 32.4 yrs Mean 15.3 yrs	4.75 yrs – 18. 6 yrs Mean 9. 3 yrs	• Medulloblastoma (12) • Ependymoma (6)	Surgery (18) RT (18) Chemotherapy (14) Shunts VP (9)	WAIS-R, WISC -R, McCarthy Scales, WRAT-R , Washington Structured Psychosocial Review & Inventory, Adolescent Psychological	17 pts. Attended school. IQ declined > 10 points for 4-6 subjects in first 5 yrs following TX. Significant decline in IQ > 20 points in 4-5 subjects < 6 yrs at diagnosis. 2-3 subjects > 6 yrs at diagnosis had stable IQ's. 17 subjects administered WRAT-R had borderline performance in reading & spelling & deficient performance in arithmetic. Impaired psychosocial adjustment correlated significantly with greater time since TX. Impaired academic

							Inventory, Symptom Checklist 90-R, Child Behaviour Checklist, Hollingshead Two Factor Index of Social Position; Holroyd Questionnaire on Resources & Stress-Short Scale;	achievement correlated with young age at diagnosis.. Psychosocial adjustment rated as normal. Significant family problems reported on life span care, home health care, financial stress & stress of terminal illness. Quality of life acceptable.
Syndikus, Tait, Ashley & Jannoun, 1994 N = 156	R Parametric Logistic regression using step wise procedure.	Median 2.8 yrs	7-42 yrs	35 yrs	• Supratentorial (30) • Ependymoma (2) • Astrocytoma (7) • Optic glioma (10) • Craniopharyngioma (6) • Other (5) • Infratentorial (27) • Medulloblastoma (13) • Ependymoma (9) • Astrocytoma (3) • Other (2)	Supratentorial Surgery (17) RT (30) Chemo (3) Infratentorial Surgery (26) RT (27) Chemo (9)	WISC-R WART MRC neurological status Bloom Scale	89 pts deceased, 67 pts survived, 57 pts tested Neurological impairment shown in 25% of sample, but more common in Supratentorial Grp. Endocrine dysfunction found in 78% of sample., more marked in parasellar tumours. 39% of all the children are mentally retarded. No correlation found between year of diagnosis, age at treatment, presence of hydrocephalus, addition of chemotherapy, radiation dose or volume and severity of intellectual impairment. Multivariate analysis showed that epilepsy is the only significant variable associated with poor cognitive function. Long term morbidity found to be disabling in 58% of survivors.
Chadderton *et*	R				• Low Grade Astrocytoma	Surgery (50)	WISC-R,	There was no difference

al., 1995 N=50	Non Parametric Mann Whitney U test	1 yr to 14 yrs Median 7 yrs 1 yr to 14 yrs Median 7 yrs 1 yr to 14 yrs Median 5.5 yrs 1 yr to 14 yrs Median 5.5 yrs		4 – 25 yrs Median 14 3 – 25 yrs Median 8 yrs 6 – 25 yrs Median 18 yrs 1 –14 yrs Median 8 yrs	(whole sample =50) • All Subdivided: • Superficial Astrocytoma (17) • Deep Astrocytoma tumours (8) • Superficial Astrocytoma (22) • Deep Astrocytoma (3)	RT (39) Sample: Surgery & RT Grp (25) Surgery & No RT (25) Cerebellar Sub Grp: Surgery & RT (14) Surgery & No RT (18)	WAIS, Schonell Graded Reading, Adult Memory & Information Processing Battery.	in neurological function between those TX with Surgery & RT & those TX with Surgery only in both Whole Grp & the subgroup i.e. Cerebellar Grp. In the Whole Grp scores of Surgery & RT TX Grps worse than those TX by Surgery only where significant differences were shown in IQ & information processing. Children TX with Surgery & RT < 5 yrs old at diagnosis significantly worse than those not treated with RT. Age at diagnosis was not a significant factor in the cerebellar sub group. Special schooling required for 40% of sample as a Whole TX with Surgery & RT & for 36% of Cerebellar Sub Grp Cerebellar Sub Grp: Significant differences between Surgery & RT Grp & Surgery only grp in IQ, information processing scores & visual memory test scores. The difference was 22 points in FSIQ 16 points in VIQ & 27 points in PIQ between pts TX with Surgery & RT & those TX with Surgery only. Presence of posterior fossa tumour per se does not appear to produce significant intellectual decline as those TX with Surgery only appear to have little impact on test scores whereas an IQ decline was shown in those TX with Surgery & RT.
Chapman, Waber,	R	.9 yrs – 14 yrs.	Not given	4 yrs to 20 yrs Median 10 yrs	• Posterior Fossa Tumours:	Cranial Irradiation (15)	WISC-R, WAIS-R, Rey	Earlier age at diagnosis associated with neurologic impairment.

Bernstein *et al.*, 1995 N = 15	Non Parametric Pearson Product Moment	Mean 5.66 yrs			• Medulloblastoma (13) • Ependymoma (2)	Surgery (14)	Complex Figure, California Verbal Learning Test, Boston Naming Test, Word Fluency Test, WMS, Grooved Peg Board, Write a Passage, Repeated Graphomotor Patterns, WRAT-R	Perioperative summary score strongly associated with poor neuropsychological outcome. Early age diagnosis < 6 yrs associated with a higher prevalence of obtunduration at presentation, hydrocephalus & surgery involving structures outside vermis. Tumour location & perioperative factors not related to age at diagnosis. Authors note that it is not possible to discern whether outcomes represent a combined impact of perioperative complications and early RT or whether complications though associated with age at diagnosis are not causal. Poor neurobehavioural outcomes may be related to more aggressive tumour growth or complications of initial therapy and not solely due to toxicity from RT.
Hoppe-Hirsch, Brunet, Laroussinie *et al.*, 1995 N = 96	R Tested at 1 yr, 5 yrs 10 yrs Post TX Descriptive	< 16 yrs of age	Not given	2 yrs – 18 yrs. Median 5 yrs	• Posterior Fossa • Medulloblastoma (59) • Ependymoma (37)	Medulloblastoma Grp Surgery (59) WBRT (59) RT to posterior fossa (59) Chemotherapy (45) Ependymoma Grp: Surgery (37) RT to posterior fossa (28) Chemotherapy (10)	Test battery not specified. IQ level, school performance and behaviour rated.	Neurological sequelae the same for both Grps. 50% of pts mild to moderate cerebellar syndrome, 9pts severe visual disturbances, 5 pts severe hearing loss at 5 & 10 yr assessments. IQ: Performance of Ependymoma Grp remained stable over the yrs with 56% with FSIQ > 90 at 10 yrs post TX. Medulloblastoma Grp deteriorated over the yrs 43% of the Grp had FSIQ < 90 in year 1 post TX, 22% in year 5 & 10% in year 10. The same pattern evident in school performance Ependymoma Grp 60-

								70% attended normal school, but 20% had difficulties. Medulloblastoma Grp 43% at normal school 5 yrs post TX but this declined to 17% at year 10. Behaviour problems found in 20% of both Grps 1 to 2 yrs after TX, these remained stable in the Ependymoma Grp but regressed in the Medulloblastoma Grp to 40% at 5 yrs post TX & 56% at 10 yrs post TX. Post operative complications at 1 yr for both Grps showed 76% of subjects who had no complications had IQ's > 90 whereas 28% who had complications had IQ's < 90 at 5 to 10 yrs post TX. Intraoperative cardiovascular complications correlated with FSIQ < 90 5 to 10 yrs post TX. Authors conclude that progressive deterioration is due to WBRT, post operative and intraoperative complications. However the contribution of chemotherapy to the sequelae is not discussed. In addition the total number of subjects at each time of examination are not given and only percentages are reported. This implies that the results may not be as dramatic as subject numbers would have lessened over a 10 yrs period.
Jordan, Murdoch, Buttsworth et al. ,1995 N=40	R 4 Grps: Closed Head Injury	5.5-12.9 yrs	7 – 17 yrs 5.05 – 12.09 yrs	Not given	• Severe Closed Head Injury (10)	GCS score 3-8 On admission PFT:	Extensive Speech & Language Battery	Performance of experimental grps compared to control grps matched for age, sex and education. In all three Grps areas of language competence were compromised by the various brain injuries & all Grps

	PFT Grp ALL Grp Control Grp Parametric Manova	1.09 – 13.03 yrs 2.11 yrs – 8 yrs	7 – 15.07 yrs 6.04 -16 yrs matched for age		• Posterior Fossa Tumours (10) • ALL (10) • Control Grp (10)	Surgery (10) RT (7) Chemo (1) ALL: RT +Chemo (10)		achieved poorer scores than Control Grps. Motor speech skills were spared for all experimental grps except for 2 subjects in PFT grp. Outcome shows that there is a similarity in language impairment in the 3 experimental grps despite TX interventions of surgery, RT & chemo.
Kimmings, Kleinlugtebeld, Casey *et al.*, 1995 N = 25	R Grp A: Children At normal school Grp B: Children at special school. Descriptive	Grp A: Mean 7.6 yrs Grp B Mean 5.5yrs	Not given	2.4 yrs – 9.5 yrs Mean 6.4 yrs	• Medulloblastoma (25)	Surgery (25) RT (25)	Not formally tested. Evaluation of Child's performance at school Mainstream versus Special school.	56% of the sample attended mainstream education without any need for remedial help. 44% required remedial help in a normal school or attended special school. Differences in academic potential related to age 7 yrs at diagnosis and the presence of post-operative complications i.e. the need for a shunt, large ventricular size & growth hormone replacement. The authors note that the sample had few young children (9/25) < 5ys old at diagnosis. This had the potential to increase the threshold at which age at diagnosis became significant in the evaluation of school placement.
Dennis, Spiegler, Hetherington *et al.*, 1996 N = 25	R Parametric ANOVA	0.27 – 12.19 yrs Mean 5.38 yrs		0.82 –15.69 yrs Mean 6.16 yrs	• Medulloblastoma (25)	Surgery (25) RT (25) Chemotherapy (7)	WISC	Age at diagnosis and Time since Treatment made separate contributions to intellectual morbidity. PIQ appeared to measure some general effects of diffuse cerebral insult because it varied with chronological age of child at tumour diagnosis but was relatively constant in magnitude once established. VIQ

								less sensitive to age at diagnosis but declined with time since treatment.
Lazareff & Castro- Sierra, (1996) N = 13	P Midline Tumour Grp Hemispheric Grp Control Sibling Grp Test pre & post-op. 4 mths post surgery & 24 mths post surgery. (n=1) Non Parametric Wilcoxon Test	Midline Grp: 5 yrs – 13 yrs Hemispheric Grp: 10 yrs – 11 yrs Control Grp: 7 yrs – 14 yrs		3 days – 24 months	Midline Grp: - • Medulloblastoma (3) • Juvenile Astrocytoma (1) • Ependymoma (1) Hemispheric Grp:- • Medulloblastoma (2) • Astrocytoma (2) Control Group:- • Siblings (4)	Surgery (9) RT (9)	Small Plastic Toys, Different Shapes for Visual & Auditory memory.	Auditory memory performance statistically worse in tumour patients than controls. Type of surgery & site of tumour not related to number of errors in any tested categories. The one child tested 2 yrs post surgery showed progressive improvement in performance of visual & auditory memory. Authors propose the results provide evidence that the cerebellum plays a role in integration of auditory stimuli.
Whitton, Rhydderch, Furlong *et al.*, 1997 N = 50	P Non Parametric Chi Square	Not given	19 yrs – 81 yrs Mean 47 yrs	Not given	• Supratentorial (40) • Infratentorial (10)	Surgery (48) WBRT (3) Local RT (44) Chemotherapy (14)	Health Utilities Index Mark 2 & Mark 3	Questionnaire completed by 90% of respondents. 10% of respondents did not report some form of morbidity & 80% reported multiple impairments. Most prevalent were in the attributes of sensation, emotion and cognition. 50% reported pain.
Yang, Wong, Cheng *et al.*,	R	2-14 yrs Mean 6.16	Not given	0.3-14 yrs Mean 5.97 yrs	• Medulloblastoma (19)	Surgery (19) RT (16)	Bloom Classification	10 classified as no disability performance status & 7 as minimal

1997 N = 19	Non Parametric	yrs				Shunts for ICP (12) Chemotherapy (11)	of Disability, Binet, Leiter International Performance Scale, WISC-R	disability. 2 incapable of self-care. 11 normal intelligence, 3 borderline intelligence, 4 mild mental retardation, 1 moderate mental retardation. Mean FSIQ = 85,VIQ = 90, PIQ =85. No significant difference between presence of hydrocephalus (FSIQ=83) & absence of hydrocephalus (FSIQ=90). Significant negative correlation between IQ score & WBRT & between Years since Treatment and RT.
Bauld, Anderson & Arnold,1998 N = 66	R Adolescent Random Controls (34) Parametric ANOVA, t test, Multiple Regression analysis.	Mean 7.5 yrs	Pts Mean 14.9 yrs Controls Mean 14.7 yrs	Mean 8 yrs	• ALL (32)	Chemotherapy & RT (17) Chemotherapy only (10) Chemotherapy with combination of other modalities (4) Unknown (1)	Demographic Questionnaire, Subjective Coping Levels, Strait-Trait Anxiety inventory, Adolescent Coping Scale, Self-Description Questionnaire.	Cancer survivors have similar psychosocial profiles to controls but are more likely to use avoidance strategies to manage problems. Age diagnosis & time since treatment strong predictors of outcome. Specifically older adolescents more prone to worry than younger adolescence. Authors note that it is important to understand psychosocial status of survivors to optimise their quality of life
Dennis, Hetherington & Spiegler, 1998 Three Studies: Focused & Selective Attention N = 31	R Parametric z scores, ANOVA	Mean 7 yrs		Mean 4.8 yrs	• Third Ventricle Tumours (17) • Fourth Ventricle Tumours (14)	No RT (21) RT (12)	WISC-R Gordon Diagnostic System	Tumour subjects TX with RT performed more poorly than those TX with No RT on both focused & selective attention tasks. Later age at diagnosis correlated significantly with higher selective attention scores. Shorter time since treatment correlated significantly with higher focused attention scores &

Working Memory N = 64 Implicit Memory N = 15	ANOVA ANOVA	Mean 8.3 yrs Children & adolescents		Mean 5.9 yrs Not given	• Third Ventricle (46) • Fourth Ventricle (18) • Third Ventricle or Brain Stem tumours (15) • Controls (15) matched for age • & sex	No RT (38) RT (26) RT (9)	Recognition Memory Task	higher selective attention scores. ANOVA for working memory by both tumour location and RT showed no effect for location but showed a significant main effect for RT. Analysis of interaction showed RT effect more pronounced in posterior Third Ventricle Grp and to some extent in Fourth Ventricle Grp. Age at Diagnosis & Time since Treatment were not correlated with working memory. Both tumour & control Grps had high levels of explicit recognition after 1 hr. Tumour subjects showed less priming than controls when tested under full or divided attention. No correlation between age at test and memory measures.
Jenkin, Danjoux. & Greenberg, 1998 N = 222	R Descriptive	< 4 yrs	> 21 yrs	37 yrs	• Primary tumours (23) Number of subjects of each tumour type not given: • Astrocytoma low grade • Astrocytoma high grade • Ependymoma • Other types	Surgery (number not given) RT(number not given)	Quality of Life assessed by neurological clinical examination & Questionnaire	10 year survival rate =40%. Only 23 survivors tested. Quality of Life described as not good as only 1 of every 3 survivors had a normal life style. Shortfall was focal neurological deficits in the domain of motor functions, ambulation, vision & hearing, which impaired ability to attend normal schooling. Thus only 1 in 3 survivors will be able to live normal competitive lives.
Grill, Renaux, Bulteau *et al.*,	R	5-15 yrs mean = 5.7	Mean = 11.4 yrs	Mean = 5.3 yrs	• Posterior Fossa Tumours • Medulloblastoma (19)	Surgery (19) Chemotherapy:	WPPSI-R WISC-11	Significant correlation between FSIQ & CSI dose

1999 N = 31	Parametric : t test ANOVA	yrs			• Ependymoma (12)	Medullo (17) Ependymoma (4) Subjects divided into 3 Grps according to CSI dose: Grp 1 = 0 Gy (11) Grp 2 = 25 Gy (11) Grp 3 = 35 Gy (9)	Kaufman-ABC Purdue Pegboard	FSIQ 84.5 correlated with 0 Gy dose FSIQ 76.9 correlated with 25 Gy dose FSIQ 63.7 correlated with 35 Gy dose Chemotherapy not associated with impaired intellectual outcome. Verbal comprehension scores lower in children who had received higher CSI doses. No correlation between neuropsych test scores & age at radiotherapy, years since treatment , disease presentation and post operative complications. Correlation between FSIQ & SES just short of significance, trend higher FSIQ in wealthier subjects Tumour type, presence of metastasis or incomplete resection correlated with radiation dose & therefore associated with poorer intellectual outcome.
Mulhern, Reddick, Palmer et al. 1999 N = 36	R Parametric t test, Pearson Product Moment	< 21 years Subjects age matched between groups mean age difference =3.7 months		LGA GRP = 2.6 yrs	• Medulloblastoma (MED =18) • Low Grade Astrocytoma Posterior Fossa • Tumours (LGA =18)	MED GRP: Surgery (18) CRT (18) Chemo (9) LGA GRP: Surgery (18)	WISC –111 WAIS-R	MRI Segmentation protocol done on all subjects and analyzed with FSIQ. MED GRP significantly less normal white matter volumes on MRI and lower FSIQ 82 compared to LGA GRP FSIQ 92.9. CRT with or without chemotherapy induced destruction of normal white matter volumes which can partially explain intellectual and academic deficits in medulloblastoma survivors. Results suggests that normal white matter is essential for IQ development. The obtained model suggests that variations in the

								patient's normal white matter may provide a more direct explanation for variations in FSIQ than patient's age at treatment.
Noll, Gartstein Vannatta *et al.*, 1999 N = 76	R Matched Sibling Control (n=76) Parametric: ANOVA	Not given	Pts Mean 11.5 yrs	Average 0.9 yrs	• Leukaemia (38) • Lymphoma (23) • Solid tumours, • not CNS tumours (15)	Chemotherapy (76)	CBCL, Revised Class Play, Child Depression Inventory Roberts Apperception Test for Children.	Pts and Controls similar on measures of emotional well-being. Pts better on dimensions of social functioning. Considerable psychological hardiness present in pts.
Hetherington. Dennis & Spiegler, 2000 N=80	R Age Matched Controls (40) Parametric ANOVA	Astrocytoma Mean=7.6 yrs Medulloblastoma mean = 8 yrs	Mean 20 .3 yrs Mean 23.7 yrs Mean 23 yrs	Mean 12.5 yrs Mean 15.8 yrs	• Cerebellar Astrocytoma (20) • Medulloblastoma (20)	Surgery only (20) Surgery, +RT (20)	Short duration perceptions = 400 ms Long duration estimations = 30-60 minutes WISC-111 WAIS-R Digit span WMS-R (General memory index) Wide Range Assessment of Learning & Memory	No functional recovery over time of the cerebellar system that underlies short duration perception. Younger age at treatment is not a protective factor. Although no group differences present in the functional measures of long duration estimation, tumour related prospective memory deficits interfered with the ability to produce long duration prospective estimates. The utilization of sensory & somatomotor information to refine real world spatiotemporal estimates were compromised in the case of more extensive cerebellar lesions & diffuse extracerebellar secondary lesions arising from treatment for medulloblastoma group.

TABLE INDEX

ALL: Acute Lymphoblastic Leukaemia; **Bloom:** Bloom Functional Rating Scale; **Beery** : Beery Developmental Scales of Visual Motor Integration; **CBCL**: Child Behaviour Checklist; **Claesson-Dahl**: Swedish Learning Test; **Cronholm-Molder** : Swedish Memory Test; **CPT**: Continuous Performance Test;**CRT:** Cranial Radiation Therapy; **CSI:** Craniospinal Irradiation; **FSIQ** : Full-scale Intelligence Quotient; **HSPP** : Harter Self Perception Profiles; **ITPA**: Illinois Test of Psycholinguistic Abilities; **LBC**: Louisville Behaviour Checklist; **LLNB** : Luria Nebraska Neuropsychological Battery; **MSCA**: McCarthy Scale of Children's Abilities; **MMPI**; Minnesota Multiphasic Personality Inventory; **NDC** : Neurologic Dysfunction's of Children: **P**: Prospective ; **PIAT** : Peabody Individual Achievement Test;

pts: patients; **PIC**; Personality Inventory for Children; **R**: Retrospective; **RAVLT**: Rey Auditory Verbal Learning Test; **RFRT :** Restricted Field Radiotherapy; **RFRT :** Restricted Field Radiotherapy; **SDCT**; Slossom Drawing Co-ordination Test; **SR**: Selective Reminding; **SRB** : Swedish Adult IQ Test; **TMT A & B**; Trail Making Test A & B; **TX**: Treatment; **WAIS**: Wechsler Adult Intelligence Scale: ; **WBRT** · Whole Brain Radiation Therapy; **WCST**: Wisconsin Card Sorting Test; **WISC**: Wechsler Intelligence Scale for Children; **WISC-R**: Wechsler Intelligence Scale for Children Revised; **WMS** : Weschler Memory Scale; **WMSB** . Wisconsin Motor Steadiness Battery; **WPPSI**: Wechsler Preschool and Primary Scale of Intelligence; **VABS** : Vineland Adaptive Behaviour Scales.

In most cases the categories and diagnostic terminology reflect those of the authors.
The numbers in parentheses are the number of patients in each category.